DESCRIPTION

METHOD OF TREATING OBESITY USING ANTIOXIDANT INFLAMMATION MODULATORS

BACKGROUND OF THE INVENTION

The present application claims the benefit of priority to U.S. Provisional Applications 61/389,090, filed October 1, 2010, and 61/323,276, filed April 12, 2010, the entire contents of which are incorporated herein by reference in their entireties.

I. Field of the Invention

The present invention relates generally to the fields of biology and medicine. More particularly, it concerns methods for the prevention and/or treatment of diseases, such as obesity, with antioxidant inflammation modulators (AIMs).

II. Description of Related Art

Obesity has become a major health problem in the United States and other developed nations. In the United States, 65% of the adult population is considered overweight or obese, and more than 30% of adults meet the criteria for obesity. The World Health Organization has estimated that more than 1 billion adults worldwide are overweight, with 300 million of these considered clinically obese (Hotamisligil, 2006). The incidence of obesity in children is also growing rapidly in many countries. Obesity is a major risk factor for cardiovascular disease, stroke, insulin resistance, type 2 diabetes, liver disease, neurodegenerative disease, respiratory diseases and other severe illnesses, and has been implicated as a risk factor for certain types of cancer including breast and colon cancer. Aside from its impacts on physical health, obesity has significant adverse effects on quality of life and psychological well-being. The incidence of obesity, already high, is likely to grow as a result of increasingly sedentary lifestyles in many countries. In addition, certain widely used psychiatric drugs, notably atypical antipsychotics, are associated with weight gain and increased risk of diabetes. Since these drugs must be used chronically to achieve adequate control of psychiatric symptoms, and treatment compliance in patients with mental disorders is frequently poor, these side effects present both a barrier to compliance and a significant additional health risk to patients.

Although it is well established that weight loss can be achieved through reduced caloric intake and increased physical activity, obesity has continued to be an intractable problem in Western countries, especially in the United States. The discovery of safe and

effective drugs to induce weight loss has been a major research goal for decades. However, to date the drugs that have shown efficacy have been burdened with significant side effects or have shown only modest efficacy. For example, amphetamines have been used effectively as appetite suppressants but have a strong risk of dependence along with other side effects. The discovery of leptin, a peptide hormone that plays a major role in appetite regulation, was considered to be a potential breakthrough in the treatment of obesity, but in clinical trials, leptin was not effective. More recently, cannabinoid receptor antagonists were under development as anti-obesity drugs but showed unacceptable psychiatric side effects. Similarly, drugs designed to reduce fat absorption in the digestive tract have been associated with significant gastrointestinal side effects.

Accordingly, there is a significant need for new anti-obesity treatments. In particular, there is a need for anti-obesity treatments with limited side effects that may be safely used in combination with other drugs that are in common use in obese patients, such as antidiabetic drugs, antihypertensive drugs, cholesterol-reducing agents, and insulin. Thus, agents that can be used for the treatment of obesity would represent a significant advance.

SUMMARY OF THE INVENTION

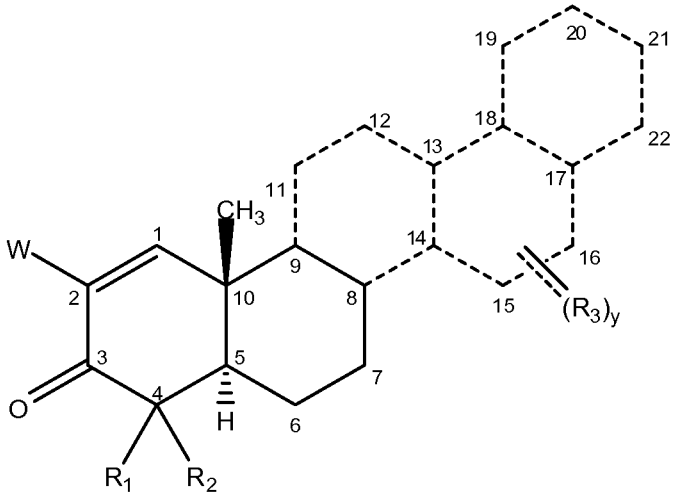
Thus, in accordance with the present invention, there are provided methods of treating overweight or obese subjects with selective activators of the antioxidant transcription factor Nrf2, such as an antioxidant inflammation modulator (AIM) so as to reduce the weight of the subject. In some aspects, there is provided a method of reducing weight in a subject in need thereof comprising administering to the subject an antioxidant inflammation modulator (AIM) in an amount sufficient to reduce the subject's weight. In some aspects, there is provided a method of pt in a subject in need thereof comprising administering to the subject an antioxidant inflammation modulator (AIM) in an amount sufficient to reduce the subject's weight.

In some embodiments, the subject has excess body fat. In some embodiments, the subject is overweight. In some embodiments, the subject's body mass index (BMI) is from 25 kg/m^2 to 30 kg/m^2. In some embodiments, the subject is obese or exhibits one of more symptoms of obesity. In some embodiments, the obesity is class I. In some embodiments, the subject's BMI is from 30 kg/m^2 to 35 kg/m^2. In some embodiments, the obesity is class II. In some embodiments, the subject's BMI is from 35 kg/m^2 to 40 kg/m^2. In some

embodiments, the obesity is class III. In some embodiments, the subject's BMI is from 40 kg/m^2 to 80 kg/m^2. In some embodiments, the subject is a human subject.

In some variations of one or more of the above embodiments, the method reduces a subject's weight by 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 25%, 30%, 35%, 40%, 45% 50%, 55%, 60% or 65%. In some variations of one or more of the above embodiments, the method also selectively induces Nrf2 in the subject. In some variations of one or more of the above embodiments, the method also inhibits activation of NF-κB in the subject.

In some variations of one or more of the above embodiments, the AIM is a compound of the formula:



,

wherein:

W is an electron withdrawing group;

R_1 and R_2 are each independently:

hydrogen, hydroxy, $alkyl_{(C\leq 8)}$, substituted $alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, substituted $alkenyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$ or substituted $alkoxy_{(C\leq 8)}$; or

R_1 and R_2 are taken together and are $alkanediyl_{(C\leq 18)}$, $alkenediyl_{(C\leq 18)}$, $arenediyl_{(C\leq 18)}$, $alkoxydiyl_{(C\leq 18)}$, $alkenyloxydiyl_{(C\leq 18)}$, $alkylaminodiyl_{(C\leq 18)}$, $alkenylaminodiyl_{(C\leq 18)}$, or $alkenylaminooxydiyl_{(C\leq 18)}$;

each R_3 is independently:

hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio;

$alkyl_{(C\leq 12)}$, $alkenyl_{(C\leq 12)}$, $alkynyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $alkylidene_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$,

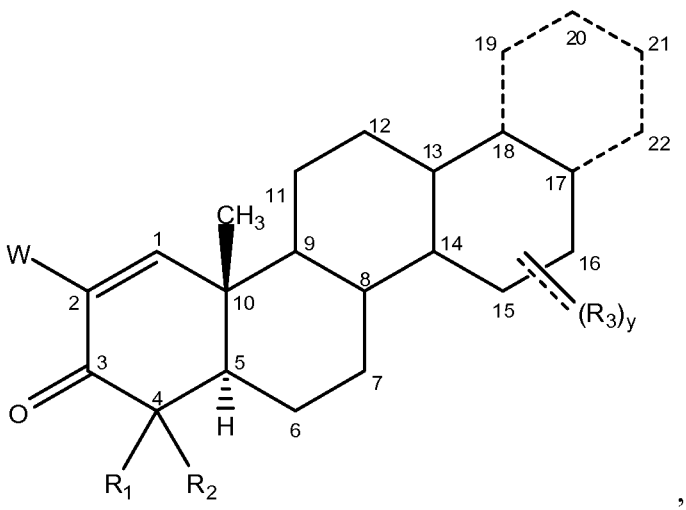
alkenyloxy$_{(C\leq12)}$, alkynyloxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, heteroaralkoxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, alkoxyamino$_{(C\leq12)}$, alkenylamino$_{(C\leq12)}$, alkynylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, heteroaralkylamino$_{(C\leq12)}$, alkylsulfonylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, alkylimino$_{(C\leq12)}$, alkenylimino$_{(C\leq12)}$, alkynylimino$_{(C\leq12)}$, arylimino$_{(C\leq12)}$, aralkylimino$_{(C\leq12)}$, heteroarylimino$_{(C\leq12)}$, heteroaralkylimino$_{(C\leq12)}$, acylimino$_{(C\leq12)}$ or a substituted version of any of these groups; or

any two R_3 in $(R_3)_y$ are taken together and are alkanediyl$_{(C\leq18)}$, alkenediyl$_{(C\leq18)}$, arenediyl$_{(C\leq18)}$, alkoxydiyl$_{(C\leq18)}$, alkenyloxydiyl$_{(C\leq18)}$, alkylaminodiyl$_{(C\leq18)}$, alkenylaminodiyl$_{(C\leq18)}$, or alkenylaminooxydiyl$_{(C\leq18)}$; and

y is from 0 to 8;

or a pharmaceutically-acceptable salt or tautomer thereof.

In some variations of one or more of the above embodiments, the AIM is a compound of the formula:



,

wherein:

W is an electron withdrawing group;

R_1 and R_2 are each independently:

hydrogen, hydroxy, alkyl$_{(C\leq8)}$, substituted alkyl$_{(C\leq8)}$, alkenyl$_{(C\leq8)}$, substituted alkenyl$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$ or substituted alkoxy$_{(C\leq8)}$; or

R_1 and R_2 are taken together and are alkanediyl$_{(C\leq 18)}$, alkenediyl$_{(C\leq 18)}$, arenediyl$_{(C\leq 18)}$, alkoxydiyl$_{(C\leq 18)}$, alkenyloxydiyl$_{(C\leq 18)}$, alkylaminodiyl$_{(C\leq 18)}$, alkenylaminodiyl$_{(C\leq 18)}$, or alkenylaminooxydiyl$_{(C\leq 18)}$;

each R_3 is independently:

hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio;

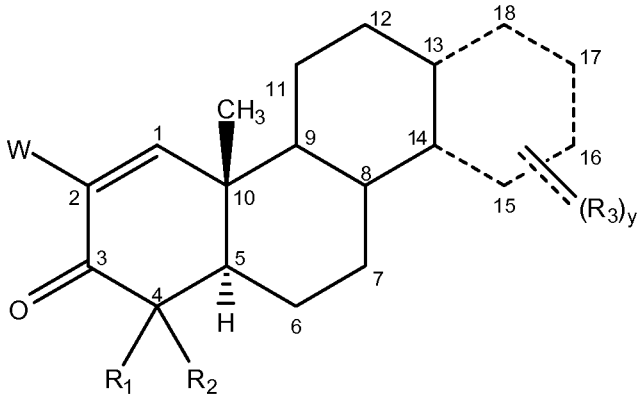
alkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, alkylidene$_{(C\leq 12)}$, alkoxy$_{(C\leq 12)}$, alkenyloxy$_{(C\leq 12)}$, alkynyloxy$_{(C\leq 12)}$, aryloxy$_{(C\leq 12)}$, aralkoxy$_{(C\leq 12)}$, heteroaryloxy$_{(C\leq 12)}$, heteroaralkoxy$_{(C\leq 12)}$, acyloxy$_{(C\leq 12)}$, alkylamino$_{(C\leq 12)}$, dialkylamino$_{(C\leq 12)}$, alkoxyamino$_{(C\leq 12)}$, alkenylamino$_{(C\leq 12)}$, alkynylamino$_{(C\leq 12)}$, arylamino$_{(C\leq 12)}$, aralkylamino$_{(C\leq 12)}$, heteroarylamino$_{(C\leq 12)}$, heteroaralkylamino$_{(C\leq 12)}$, alkylsulfonylamino$_{(C\leq 12)}$, amido$_{(C\leq 12)}$, alkylimino$_{(C\leq 12)}$, alkenylimino$_{(C\leq 12)}$, alkynylimino$_{(C\leq 12)}$, arylimino$_{(C\leq 12)}$, aralkylimino$_{(C\leq 12)}$, heteroarylimino$_{(C\leq 12)}$, heteroaralkylimino$_{(C\leq 12)}$, acylimino$_{(C\leq 12)}$ or a substituted version of any of these groups; or

any two R_3 in $(R_3)_y$ are taken together and are alkanediyl$_{(C\leq 18)}$, alkenediyl$_{(C\leq 18)}$, arenediyl$_{(C\leq 18)}$, alkoxydiyl$_{(C\leq 18)}$, alkenyloxydiyl$_{(C\leq 18)}$, alkylaminodiyl$_{(C\leq 18)}$, alkenylaminodiyl$_{(C\leq 18)}$, or alkenylaminooxydiyl$_{(C\leq 18)}$; and

y is from 0 to 8;

or a pharmaceutically-acceptable salt or tautomer thereof.

In some variations of one or more of the above embodiments, the AIM is a compound of the formula:



,

wherein:

W is an electron withdrawing group;

R_1 and R_2 are each independently:

hydrogen, hydroxy, $alkyl_{(C\leq 8)}$, substituted $alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, substituted $alkenyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$ or substituted $alkoxy_{(C\leq 8)}$; or

R_1 and R_2 are taken together and are $alkanediyl_{(C\leq 18)}$, $alkenediyl_{(C\leq 18)}$, $arenediyl_{(C\leq 18)}$, $alkoxydiyl_{(C\leq 18)}$, $alkenyloxydiyl_{(C\leq 18)}$, $alkylaminodiyl_{(C\leq 18)}$, $alkenylaminodiyl_{(C\leq 18)}$, or $alkenylaminooxydiyl_{(C\leq 18)}$;

each R_3 is independently:

hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio;

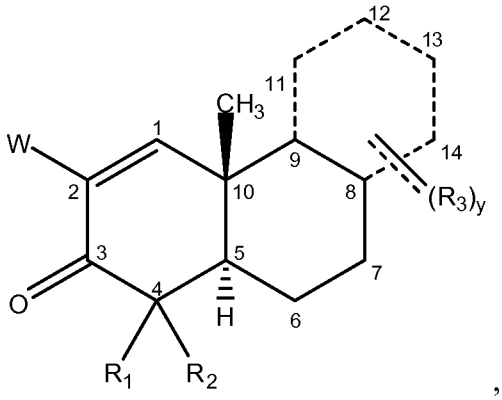
$alkyl_{(C\leq 12)}$, $alkenyl_{(C\leq 12)}$, $alkynyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $alkylidene_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$, $alkenyloxy_{(C\leq 12)}$, $alkynyloxy_{(C\leq 12)}$, $aryloxy_{(C\leq 12)}$, $aralkoxy_{(C\leq 12)}$, $heteroaryloxy_{(C\leq 12)}$, $heteroaralkoxy_{(C\leq 12)}$, $acyloxy_{(C\leq 12)}$, $alkylamino_{(C\leq 12)}$, $dialkylamino_{(C\leq 12)}$, $alkoxyamino_{(C\leq 12)}$, $alkenylamino_{(C\leq 12)}$, $alkynylamino_{(C\leq 12)}$, $arylamino_{(C\leq 12)}$, $aralkylamino_{(C\leq 12)}$, $heteroarylamino_{(C\leq 12)}$, $heteroaralkylamino_{(C\leq 12)}$, $alkylsulfonylamino_{(C\leq 12)}$, $amido_{(C\leq 12)}$, $alkylimino_{(C\leq 12)}$, $alkenylimino_{(C\leq 12)}$, $alkynylimino_{(C\leq 12)}$, $arylimino_{(C\leq 12)}$, $aralkylimino_{(C\leq 12)}$, $heteroarylimino_{(C\leq 12)}$, $heteroaralkylimino_{(C\leq 12)}$, $acylimino_{(C\leq 12)}$ or a substituted version of any of these groups; or

any two R_3 in $(R_3)_y$ are taken together and are alkanediyl$_{(C\leq 18)}$, alkenediyl$_{(C\leq 18)}$, arenediyl$_{(C\leq 18)}$, alkoxydiyl$_{(C\leq 18)}$, alkenyloxydiyl$_{(C\leq 18)}$, alkylaminodiyl$_{(C\leq 18)}$, alkenylaminodiyl$_{(C\leq 18)}$, or alkenyl-aminooxydiyl$_{(C\leq 18)}$; and

y is from 0 to 7;

or a pharmaceutically-acceptable salt or tautomer thereof.

In some embodiments, the AIM is a compound of the formula:



,

wherein:

W is an electron withdrawing group;

R_1 and R_2 are each independently:

hydrogen, hydroxy, alkyl$_{(C\leq 8)}$, substituted alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, substituted alkenyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$ or substituted alkoxy$_{(C\leq 8)}$; or

R_1 and R_2 are taken together and are alkanediyl$_{(C\leq 18)}$, alkenediyl$_{(C\leq 18)}$, arenediyl$_{(C\leq 18)}$, alkoxydiyl$_{(C\leq 18)}$, alkenyloxydiyl$_{(C\leq 18)}$, alky-laminodiyl$_{(C\leq 18)}$, alkenylaminodiyl$_{(C\leq 18)}$, or alkenylaminooxydiyl$_{(C\leq 18)}$;

each R_3 is independently:

hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio;

alkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, alkylidene$_{(C\leq 12)}$, alkoxy$_{(C\leq 12)}$, alkenyloxy$_{(C\leq 12)}$, alkynyloxy$_{(C\leq 12)}$, aryloxy$_{(C\leq 12)}$, aralkoxy$_{(C\leq 12)}$, heteroaryloxy$_{(C\leq 12)}$, heteroaralkoxy$_{(C\leq 12)}$, acyloxy$_{(C\leq 12)}$, alkylamino$_{(C\leq 12)}$, dialkylamino$_{(C\leq 12)}$, alkoxyamino$_{(C\leq 12)}$, alkenylamino$_{(C\leq 12)}$, alkynylamino$_{(C\leq 12)}$, arylamino$_{(C\leq 12)}$, aralkyl-amino$_{(C\leq 12)}$, heteroarylamino$_{(C\leq 12)}$, heteroaralkylamino$_{(C\leq 12)}$, alkyl-

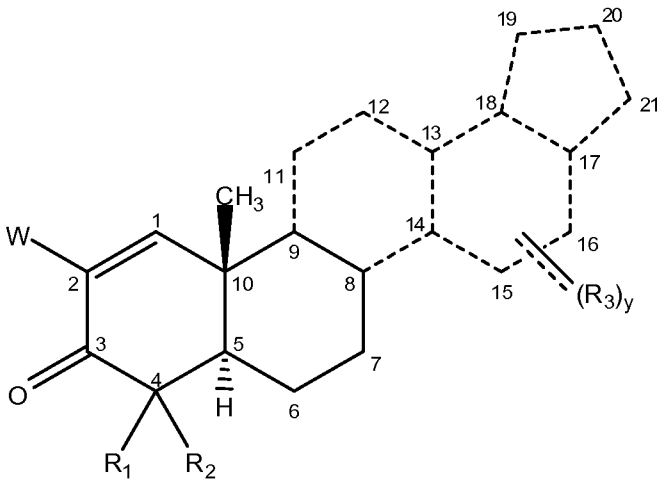
sulfonylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, alkylimino$_{(C\leq12)}$, alkenylimino$_{(C\leq12)}$, alkynylimino$_{(C\leq12)}$, arylimino$_{(C\leq12)}$, aralkylimino$_{(C\leq12)}$, heteroarylimino$_{(C\leq12)}$, heteroaralkylimino$_{(C\leq12)}$, acylimino$_{(C\leq12)}$ or a substituted version of any of these groups; or

any two R_3 in $(R_3)_y$ are taken together and are alkanediyl$_{(C\leq18)}$, alkenediyl$_{(C\leq18)}$, arenediyl$_{(C\leq18)}$, alkoxydiyl$_{(C\leq18)}$, alkenyloxydiyl$_{(C\leq18)}$, alkylaminodiyl$_{(C\leq18)}$, alkenylaminodiyl$_{(C\leq18)}$, or alkenyl-aminooxydiyl$_{(C\leq18)}$; and

y is from 0 to 6;

or a pharmaceutically-acceptable salt or tautomer thereof.

In some variations of one or more of the above embodiments, the AIM is a compound of the formula:



,

wherein:

W is an electron withdrawing group;

R_1 and R_2 are each independently:

hydrogen, hydroxy, alkyl$_{(C\leq8)}$, substituted alkyl$_{(C\leq8)}$, alkenyl$_{(C\leq8)}$, substituted alkenyl$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$ or substituted alkoxy$_{(C\leq8)}$; or

R_1 and R_2 are taken together and are alkanediyl$_{(C\leq18)}$, alkenediyl$_{(C\leq18)}$, arenediyl$_{(C\leq18)}$, alkoxydiyl$_{(C\leq18)}$, alkenyloxydiyl$_{(C\leq18)}$, alky-laminodiyl$_{(C\leq18)}$, alkenylaminodiyl$_{(C\leq18)}$, or alkenylaminooxydiyl$_{(C\leq18)}$;

each R_3 is independently:

hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio;

alkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heteroaralkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkylidene$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, alkenyloxy$_{(C\leq12)}$, alkynyloxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, heteroaralkoxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, alkoxyamino$_{(C\leq12)}$, alkenylamino$_{(C\leq12)}$, alkynylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, heteroaralkylamino$_{(C\leq12)}$, alkylsulfonylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, alkylimino$_{(C\leq12)}$, alkenylimino$_{(C\leq12)}$, alkynylimino$_{(C\leq12)}$, arylimino$_{(C\leq12)}$, aralkylimino$_{(C\leq12)}$, heteroarylimino$_{(C\leq12)}$, heteroaralkylimino$_{(C\leq12)}$, acylimino$_{(C\leq12)}$ or a substituted version of any of these groups; or

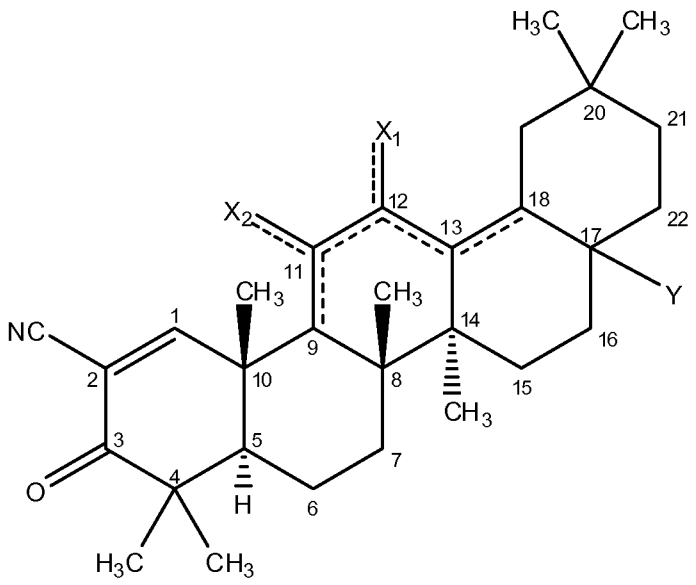
any two R_3 in $(R_3)_y$ are taken together and are alkanediyl$_{(C\leq18)}$, alkenediyl$_{(C\leq18)}$, arenediyl$_{(C\leq18)}$, alkoxydiyl$_{(C\leq18)}$, alkenyloxydiyl$_{(C\leq18)}$, alkylaminodiyl$_{(C\leq18)}$, alkenylaminodiyl$_{(C\leq18)}$, or alkenylaminooxydiyl$_{(C\leq18)}$; and

y is from 0 to 8;

or a pharmaceutically-acceptable salt or tautomer thereof.

In some variations of one or more of the above embodiments, W is cyano, fluoro or $-CF_3$.

In some variations of one or more of the above embodiments, the AIM is a compound of the formula:



wherein:

X_1 and X_2 are independently:

hydrogen, hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio; or

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkylidene_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $alkenyloxy_{(C\leq12)}$, $alkynyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heteroaralkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkoxyamino_{(C\leq12)}$, $alkenylamino_{(C\leq12)}$, $alkynylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $heteroaralkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, $alkylimino_{(C\leq12)}$, $alkenylimino_{(C\leq12)}$, $alkynylimino_{(C\leq12)}$, $arylimino_{(C\leq12)}$, $aralkylimino_{(C\leq12)}$, $heteroarylimino_{(C\leq12)}$, $heteroaralkylimino_{(C\leq12)}$, $acylimino_{(C\leq12)}$ or a substituted version of any of these groups;

Y is hydrogen, hydroxy, halo, amino, hydroxyamino, nitro, cyano, azido, mercapto, $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $alkenyloxy_{(C\leq12)}$, $alkynyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heteroaralkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkoxyamino_{(C\leq12)}$, $alkenylamino_{(C\leq12)}$, $alkynylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $heteroaralkylamino_{(C\leq12)}$ or $alkylsulfonylamino_{(C\leq12)}$; and

or a pharmaceutically-acceptable salt or tautomer thereof.

In some embodiments, the AIM is bardoxolone methyl. In some of the embodiments, at least a portion of the bardoxolone methyl is present as a crystalline form having an X-ray diffraction pattern (CuKα) comprising significant diffraction peaks at about 8.8, 12.9, 13.4, 14.2 and 17.4 °2θ. For example, the X-ray diffraction pattern (CuKα) is in some embodiments substantially as shown in FIG. 1A or FIG. 1B. In some of the embodiments, at least a portion of the bardoxolone methyl is present as an amorphous form having an X-ray diffraction pattern (CuKα) with a halo peak at approximately 13.5 °2θ, substantially as shown in FIG. 1C, and a T_g. In some of the embodiments, the T_g value is in the range of about

120 °C to about 135 °C. In some of the embodiments, the T_g value is in the range of about 125 °C to about 130 °C.

In some variations of one or more of the above embodiments, the sufficient amount to reduce the subject's weight is a daily dose from about 0.1 mg to about 30 mg of the AIM.

In some variations of one or more of the above embodiments, the AIM is administered orally, intraarterially or intravenously. In some variations of one or more of the above embodiments, the AIM is formulated as a hard or soft capsule or a tablet. In some variations of one or more of the above embodiments, the AIM is formulated as a solid dispersion comprising (i) the compound and (ii) an excipient, for example, the excipient may be a methacrylic acid – ethyl acrylate copolymer. In some embodiments, the ratio of the methacrylic acid – ethyl acrylate copolymer is 1:1.

In some variations of one or more of the above embodiments, the weight of the subject has been measured or will be measured. For example, in some embodiments, the weight of the subject has been measured prior to administering the AIM and will be measured after administering the AIM.

In some variations of one or more of the above embodiments, the BMI of the subject has been measured or will be measured. For example, in some embodiments, the BMI of the subject has been measured prior to administering the AIM and will be measured after administering the AIM.

In some variations of one or more of the above embodiments, the subject also suffers from renal disease, cardiovascular disease, diabetes, autoimmune disease, respiratory disease, neurodegenerative disease, liver disease, infectious disease, or cancer, or has undergone or will undergo organ or tissue transplant.

In some variations of one or more of the above embodiments, the subject does not also suffer from renal disease, cardiovascular disease, diabetes, autoimmune disease, respiratory disease, neurodegenerative disease, liver disease, infectious disease, or cancer, or has not or will not undergo transplant.

In some variations of one or more of the above embodiments, the subject has diabetes. In some variations of one or more of the above embodiments, the subject does not have diabetes. In some variations of one or more of the above embodiments, the subject exhibits one or more symptoms of diabetes. In some variations of one or more of the above embodiments, the subject does not exhibit any symptoms of diabetes. In some variations of one or more of the above embodiments, the subject has been identified as having diabetes. In some variations of one or more of the above embodiments, the subject has been identified as

not having diabetes. In some variations of one or more of the above embodiments, the level of a marker of diabetes in the subject has been measured or will be measured.

In some variations of one or more of the above embodiments, the subject has elevated levels of at least one biomarker associated with diabetes, cardiovascular disease, renal disease, fatty liver disease or metabolic syndrome. In some variations of one or more of the above embodiments, the subject does not have elevated levels of at least one biomarker associated with diabetes, cardiovascular disease, renal disease, fatty liver disease or metabolic syndrome. In some variations of one or more of the above embodiments, the subject does not have elevated levels of any biomarker associated with diabetes, cardiovascular disease, renal disease, fatty liver disease or metabolic syndrome. In some embodiments, the biomarker is a marker of insulin resistance, leptin resistance, adiponectin resistance, cardiovascular stress, or renal dysfunction. In some embodiments, the biomarker is a marker of insulin resistance. In some embodiments, the biomarker is fasting glucose or hemoglobin A1c. In some embodiments, the biomarker is a marker of leptin resistance. In some embodiments, the biomarker is a marker of adiponectin resistance. In some embodiments, the biomarker is adiponectin. In some embodiments, the biomarker is a marker of cardiovascular stress. In some embodiments, the biomarker is circulating endothelial cells or C-reactive protein. In some embodiments, the biomarker is circulating endothelial cells. In some embodiments, the biomarker is iNOS-positive circulating endothelial cells. In some embodiments, the biomarker is a marker of renal disease. In some embodiments, the biomarker is serum creatinine. In some embodiments, the biomarker is cystatin C. In some embodiments, the biomarker is uric acid.

In some variations of one or more of the above embodiments, the subject has chronic kidney disease (CKD) or exhibits one or more symptoms of CKD. In some variations of one or more of the above embodiments, the subject does not have chronic kidney disease (CKD). In some variations of one or more of the above embodiments, the subject does not exhibit any symptoms of CKD. In some variations of one or more of the above embodiments, the subject has been identified as having CKD. In some variations of one or more of the above embodiments, the subject has been identified as not having CKD. In some variations of one or more of the above embodiments, the level of a marker of CKD in the subject has been measured or will be measured. In some of the embodiments, the CKD is characterized by a serum creatinine level of 1.3-3.0 mg/DL where the subject is a human female or a serum creatinine level of 1.5-3.0 mg/DL where the subject is a human male. In some embodiments,

the CKD is stage 4. In some variations of one or more of the above embodiments, the subject does not have stage 4 chronic kidney disease (CKD).

In some variations of one or more of the above embodiments, the subject has diabetic nephropathy (DN) or exhibits one or more symptoms of DN. In some variations of one or more of the above embodiments, the subject does not have diabetic nephropathy (DN). In some variations of one or more of the above embodiments, the subject does not exhibit any symptoms of DN. In some embodiments, the subject has been identified as having DN. In some embodiments, the subject has been identified as not having DN. In some variations of one or more of the above embodiments, the level of a marker of DN in the subject has been measured or will be measured.

In some variations of one or more of the above embodiments, administering the AIM results in an improvement in estimated glomerular filtration rate (eGFR) of the subject. In some embodiments, the administering reduces the level of serum creatinine in the subject. In some embodiments, the level of serum creatinine in the blood of the subject has been measured or will be measured. In some variations of one or more of the above embodiments, the level of blood urea nitrogen (BUN) in the subject has been measured or will be measured.

In some variations of one or more of the above embodiments, the level of Adiponectin in the blood of the subject has been measured or will be measured.

In some variations of one or more of the above embodiments, the level of Angiotensin II in the subject has been measured or will be measured.

In some variations of one or more of the above embodiments, the subject has insulin resistance or exhibits one or more symptoms of insulin resistance. In some variations of one or more of the above embodiments, the subject does not have insulin resistance. In some variations of one or more of the above embodiments, the subject does not exhibit any symptoms of insulin resistance. In some embodiments, the subject has been identified as having insulin resistance. In some embodiments, the subject has been identified as not having insulin resistance. In some variations of one or more of the above embodiments, the level of a marker of insulin resistance in the subject has been measured or will be measured. In some embodiments, the level of hemoglobin A1c in the subject has been measured or will be measured. In some embodiments, a blood sugar level of the subject has been measured or will be measured. In some embodiments, the administering reduces the level of hemoglobin A1c or fasting blood glucose in the subject. In some embodiments, a fasting glucose level of the subject has been measured or will be measured. In some embodiments, the insulin sensitivity of the subject has been measured or will be measured by a hyperinsulinemic

euglycemic clamp test. In some embodiments, a glucose disposal rate (GDR) in the subject has been measured or will be measured.

In some variations of one or more of the above embodiments, the subject has glucose intolerance or exhibits one or more symptoms of glucose intolerance. In some variations of one or more of the above embodiments, the subject does not have glucose intolerance. In some variations of one or more of the above embodiments, the subject does not exhibit any symptoms of glucose intolerance. In some embodiments, the subject has been identified as having glucose intolerance. In some embodiments, the subject has been identified as not having glucose intolerance. In some variations of one or more of the above embodiments, the level of a marker of glucose intolerance in the subject has been measured or will be measured. In some embodiments, the level of hemoglobin A1c in the subject has been measured or will be measured. In some embodiments, a blood sugar level of the subject has been measured or will be measured. In some embodiments, the administering reduces the level of hemoglobin A1c or fasting blood glucose in the subject. In some embodiments, a fasting glucose level of the subject has been measured or will be measured. In some embodiments, the insulin sensitivity of the subject has been measured or will be measured by a hyperinsulinemic euglycemic clamp test. In some embodiments, a glucose disposal rate (GDR) in the subject has been measured or will be measured.

In some variations of one or more of the above embodiments, the subject has cardiovascular disease (CVD) or exhibits one or more symptoms of CVD. In some variations of one or more of the above embodiments, the subject does not have cardiovascular disease (CVD) or does not exhibit any symptoms of CVD. In some variations of one or more of the above embodiments, the subject does not exhibit any symptoms of CVD. In some variations of one or more of the above embodiments, the subject has been identified as having CVD. In some variations of one or more of the above embodiments, the subject has been identified as not having CVD. In some variations of one or more of the above embodiments, the level of a marker of CVD in the subject has been measured or will be measured.

In some variations of one or more of the above embodiments, the number of circulating endothelial cells (CECs) in the blood of the subject has been measured or will be measured. In some embodiments, the CECs are iNOS-positive circulating endothelial cells. In some embodiments, the administering also reduces the level of circulating endothelial cells in the subject. In some embodiments, the administering also reduces the level of hemoglobin A1c or fasting blood glucose in the subject.

In some variations of one or more of the above embodiments, the subject has fatty liver disease (FLD) or exhibits one or more symptoms of FLD. In some variations of one or more of the above embodiments, the subject does not have fatty liver disease (FLD) or does not exhibit any symptoms of FLD. In some variations of one or more of the above embodiments, the subject does not exhibit any symptoms of FLD. In some variations of one or more of the above embodiments, the subject has been identified as having FLD. In some variations of one or more of the above embodiments, the subject has been identified as not having FLD. In some variations of one or more of the above embodiments, the level of a marker of FLD in the subject has been measured or will be measured.

In some variations of one or more of the above embodiments, the subject has been identified as having cancer. In some variations of one or more of the above embodiments, the subject has been identified as not having cancer. In some variations of one or more of the above embodiments, the subject has been identified as having cancer and diabetes. In some variations of one or more of the above embodiments, the subject has been identified as not having cancer and/or not having diabetes.

In some variations of one or more of the above embodiments, if the sufficient amount were administered to a non-obese subject, the non-obese subject's weight would not be reduced significantly.

In some embodiments, the compound is formulated as a hard or soft capsule, a tablet, a syrup, a suspension, a solid dispersion, a wafer, or an elixir. In some variations, the soft capsule is a gelatin capsule. In variations, the compound is formulated as a solid dispersion. In some variations the hard capsule, soft capsule, tablet or wafer further comprises a protective coating. In some variations, the formulated compound comprises an agent that delays absorption. In some variations, the formulated compound further comprises an agent that enhances solubility or dispersibility. In some variations, the compound is dispersed in a liposome, an oil in water emulsion or a water in oil emulsion.

In some embodiments, the pharmaceutically effective amount is a daily dose from about 0.1 mg to about 500 mg of the compound. In some variations, the daily dose is from about 1 mg to about 300 mg of the compound. In some variations, the daily dose is from about 10 mg to about 200 mg of the compound. In some variations, the daily dose is about 25 mg of the compound. In other variations, the daily dose is about 75 mg of the compound. In still other variations, the daily dose is about 150 mg of the compound. In further variations, the daily dose is from about 0.1 mg to about 30 mg of the compound. In some variations, the daily dose is from about 0.5 mg to about 20 mg of the compound. In some

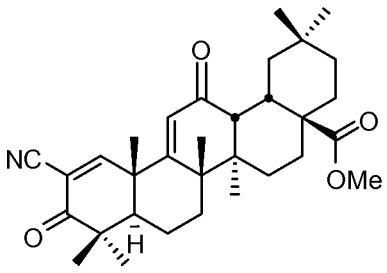
variations, the daily dose is from about 1 mg to about 15 mg of the compound. In some variations, the daily dose is from about 1 mg to about 10 mg of the compound. In some variations, the daily dose is from about 1 mg to about 5 mg of the compound.

In some embodiments, the pharmaceutically effective amount is a daily dose is 0.01 – 25 mg of compound per kg of body weight. In some variations, the daily dose is 0.05 – 20 mg of compound per kg of body weight. In some variations, the daily dose is 0.1 – 10 mg of compound per kg of body weight. In some variations, the daily dose is 0.1 – 5 mg of compound per kg of body weight. In some variations, the daily dose is 0.1 – 2.5 mg of compound per kg of body weight.

In some embodiments, the pharmaceutically effective amount is administered in a single dose per day. In some embodiments, the pharmaceutically effective amount is administered in two or more doses per day.

In some embodiments, the subject is a primate. In some variations, the primate is a human. In other variations, the subject is a cow, horse, dog, cat, pig, mouse, rat or guinea pig.

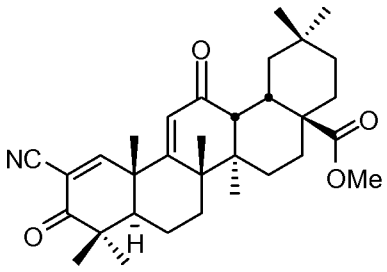
In another aspect there is provided a method of reducing a subject's weight comprising administering to the subject a compound of the formula,



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in an amount sufficient to reduce the subject's weight, where the subject has been identified as (i) being overweight or obese; and (ii) not having diabetes.

In another aspect, there is provided a method of reducing a subject's weight comprising administering to the subject a compound of the formula,



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in an amount sufficient to reduce the subject's weight, wherein:

(a) at least a portion of the compound is present as an amorphous form having an X-ray diffraction pattern (CuKα) with a halo peak at approximately 13.5°2θ, substantially as shown in FIG. 1C, and a T_g from about 120°C to about 135°C; and

(b) where the subject has been identified as

(i) being overweight or obese; and

(ii) not having diabetes.

In some embodiments, the subject is a human and the amount is a daily dose from 5 mg to 50 mg. In some embodiments, the daily dose is about 10 mg. In some embodiments, the daily dose is about 20 mg. In some embodiments, the daily dose is about 40 mg.

Other objects, features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description. Note that simply because a particular compound is ascribed to one particular generic formula does not mean that it cannot also belong to another generic formula.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present disclosure. The invention may be better understood by reference to one of these drawings in combination with the detailed description of specific embodiments presented herein.

FIGS. 1A-C – X-ray Powder Diffraction (XRPD) Spectra of Forms A and B of RTA 402. FIG. 1A shows unmicronized Form A; FIG. 1B shows micronized Form A; FIG. 1C shows Form B.

FIG. 2 – Estimated GFR Changes Over Time and Magnitude of Change in Diabetic CKD Patients Treated with Bardoxolone Methyl for 24 Weeks. Estimated GFR changes for patients by dose group at Week 24, based on results of longitudinal model, using the ITT population. Data are depicted as mean ± standard error; n = 57 (placebo, 25 mg, and 75 mg); n = 56 (150 mg).

FIG. 3 – Weight over Time by Last Dose Received. This figure compares the weight change over 52 weeks for the patient population of Examples 3 and 4. BL = baseline. W = weeks. D = days.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The current invention provides methods of using antioxidant inflammation modulators compounds that may be used, for example, to induce weight loss in patients having established obesity and complications thereof, and have limited side effects. For example, bardoxolone methyl, induces weight loss in clinically obese patients while at the same time improving measures of kidney function, glycemic control and insulin resistance, and cardiovascular disease. This combination of effects represents a significant advance in the state of the art. These and other aspects of the invention are described in greater detail below.

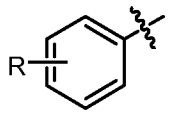
III. Definitions

When used in the context of a chemical group, "hydrogen" means −H; "hydroxy" means −OH; "oxo" means =O; "halo" means independently −F, −Cl, −Br or −I; "amino" means $-NH_2$ (see below for definitions of groups containing the term amino, *e.g.*, alkylamino); "hydroxyamino" means −NHOH; "nitro" means $-NO_2$; imino means =NH (see below for definitions of groups containing the term imino, *e.g.*, alkylimino); "cyano" means −CN; "azido" means $-N_3$; in a monovalent context "phosphate" means $-OP(O)(OH)_2$ or a deprotonated form thereof; in a divalent context "phosphate" means −OP(O)(OH)O− or a deprotonated form thereof; "mercapto" means −SH; "thio" means =S; "thioether" means −S−; "sulfonamido" means $-NHS(O)_2-$ (see below for definitions of groups containing the term sulfonamido, *e.g.*, alkylsulfonamido); "sulfonyl" means $-S(O)_2-$ (see below for definitions of groups containing the term sulfonyl, *e.g.*, alkylsulfonyl); "sulfinyl" means −S(O)− (see below for definitions of groups containing the term sulfinyl, *e.g.*, alkylsulfinyl); and "silyl" means $-SiH_3$ (see below for definitions of group(s) containing the term silyl, *e.g.*, alkylsilyl).

The symbol "−" means a single bond, "=" means a double bond, and "≡" means triple bond. The symbol "====" represents a single bond or a double bond. The symbol "〰", when drawn perpendicularly across a bond indicates a point of attachment of the group. It is noted that the point of attachment is typically only identified in this manner for larger groups

in order to assist the reader in rapidly and unambiguously identifying a point of attachment. The symbol "◄" means a single bond where the group attached to the thick end of the wedge is "out of the page." The symbol "⁞⁞⁞" means a single bond where the group attached to the thick end of the wedge is "into the page". The symbol "∿∿" means a single bond where the conformation is unknown (*e.g.*, either *R* or *S*), the geometry is unknown (*e.g.*, either *E* or *Z*) or the compound is present as mixture of conformation or geometries (*e.g.*, a 50%/50% mixture).

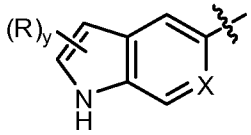
When a group "R" is depicted as a "floating group" on a ring system, for example, in the formula:



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then R may replace any hydrogen atom attached to any of the ring atoms, including a depicted, implied, or expressly defined hydrogen, so long as a stable structure is formed.

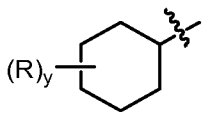
When a group "R" is depicted as a "floating group" on a fused ring system, as for example in the formula:



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then R may replace any hydrogen attached to any of the ring atoms of either of the fused rings unless specified otherwise. Replaceable hydrogens include depicted hydrogens (*e.g.*, the hydrogen attached to the nitrogen in the formula above), implied hydrogens (*e.g.*, a hydrogen of the formula above that is not shown but understood to be present), expressly defined hydrogens, and optional hydrogens whose presence depends on the identity of a ring atom (*e.g.,* a hydrogen attached to group X, when X equals −CH−), so long as a stable structure is formed. In the example depicted, R may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula above, the subscript letter "y" immediately following the group "R" enclosed in parentheses, represents a numeric variable. Unless specified otherwise, this variable can be 0, 1, 2, or any integer greater than 2, only limited by the maximum number of replaceable hydrogen atoms of the ring or ring system.

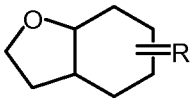
When y is 2 and "$(R)_y$" is depicted as a floating group on a ring system having one or more ring atoms having two replaceable hydrogens, *e.g.*, a saturated ring carbon, as for example in the formula:



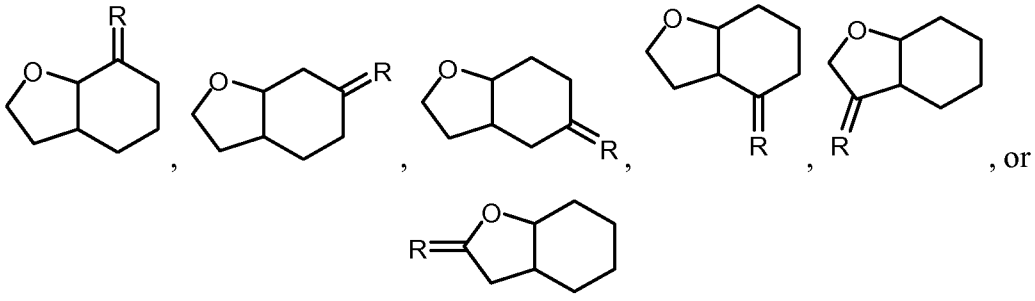
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then each of the two R groups can reside on the same or a different ring atom. For example, when R is methyl and both R groups are attached to the same ring atom, a geminal dimethyl group results. Where specifically provided for, two R groups may be taken together to form a divalent group, such as one of the divalent groups further defined below. When such a divalent group is attached to the same ring atom, a spirocyclic ring structure will result.

In the case of a double-bonded R group (*e.g.*, oxo, imino, thio, alkylidene, etc.), any pair of implicit or explicit hydrogen atoms attached to one ring atom can be replaced by the R group. This concept is exemplified below:



represents

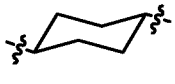


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For the groups below, the following parenthetical subscripts further define the groups as follows: "(Cn)" defines the exact number (n) of carbon atoms in the group. "(C≤n)" defines the maximum number (n) of carbon atoms that can be in the group, with the minimum number of carbon atoms in such at least one, but otherwise as small as possible for the group in question, *e.g.*, it is understood that the minimum number of carbon atoms in the group "alkenyl$_{(C\leq 8)}$" is two. For example, "alkoxy$_{(C\leq 10)}$" designates those alkoxy groups having from 1 to 10 carbon atoms (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or any range derivable therein (*e.g.*, 3 to 10 carbon atoms). (Cn-n′) defines both the minimum (n) and maximum number (n′) of carbon atoms in the group. Similarly, "alkyl$_{(C2\text{-}10)}$" designates those alkyl groups having from 2 to 10 carbon atoms (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or any range derivable therein (*e.g.*, 3 to 10 carbon atoms)).

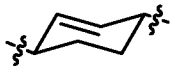
The term "alkyl" when used without the "substituted" modifier refers to a non-aromatic monovalent group with a saturated carbon atom as the point of attachment, a linear

or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. The groups, $-CH_3$ (Me), $-CH_2CH_3$ (Et), $-CH_2CH_2CH_3$ (*n*-Pr), $-CH(CH_3)_2$ (*iso*-Pr), $-CH(CH_2)_2$ (cyclopropyl), $-CH_2CH_2CH_2CH_3$ (*n*-Bu), $-CH(CH_3)CH_2CH_3$ (*sec*-butyl), $-CH_2CH(CH_3)_2$ (*iso*-butyl), $-C(CH_3)_3$ (*tert*-butyl), $-CH_2C(CH_3)_3$ (*neo*-pentyl), cyclobutyl, cyclopentyl, cyclohexyl, and cyclohexylmethyl are non-limiting examples of alkyl groups. The term "substituted alkyl" refers to a non-aromatic monovalent group with a saturated carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The following groups are non-limiting examples of substituted alkyl groups: $-CH_2OH$, $-CH_2Cl$, $-CH_2Br$, $-CH_2SH$, $-CF_3$, $-CH_2CN$, $-CH_2C(O)H$, $-CH_2C(O)OH$, $-CH_2C(O)OCH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHCH_3$, $-CH_2C(O)CH_3$, $-CH_2OCH_3$, $-CH_2OCH_2CF_3$, $-CH_2OC(O)CH_3$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2CH_2Cl$, $-CH_2CH_2OH$, $-CH_2CF_3$, $-CH_2CH_2OC(O)CH_3$, $-CH_2CH_2NHCO_2C(CH_3)_3$, and $-CH_2Si(CH_3)_3$.

The term "alkanediyl" when used without the "substituted" modifier refers to a non-aromatic divalent group, wherein the alkanediyl group is attached with two σ-bonds, with one or two saturated carbon atom(s) as the point(s) of attachment, a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. The groups, $-CH_2-$ (methylene), $-CH_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, $-CH_2CH_2CH_2-$, and , are non-limiting examples of alkanediyl groups. The term "substituted alkanediyl" refers to a non-aromatic monovalent group, wherein the alkynediyl group is attached with two σ-bonds, with one or two saturated carbon atom(s) as the point(s) of attachment, a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The following groups are non-limiting examples of substituted alkanediyl groups: $-CH(F)-$, $-CF_2-$, $-CH(Cl)-$, $-CH(OH)-$, $-CH(OCH_3)-$, and $-CH_2CH(Cl)-$.

The term "alkenyl" when used without the "substituted" modifier refers to a monovalent group with a nonaromatic carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. Non-limiting examples of alkenyl groups include: $-CH=CH_2$ (vinyl), $-CH=CHCH_3$, $-CH=CHCH_2CH_3$, $-CH_2CH=CH_2$ (allyl), $-CH_2CH=CHCH_3$, and $-CH=CH-C_6H_5$. The term

"substituted alkenyl" refers to a monovalent group with a nonaromatic carbon atom as the point of attachment, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, a linear or branched, cyclo, cyclic or acyclic structure, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The groups, −CH=CHF, −CH=CHCl and −CH=CHBr, are non-limiting examples of substituted alkenyl groups.

The term "alkenediyl" when used without the "substituted" modifier refers to a non-aromatic divalent group, wherein the alkenediyl group is attached with two σ-bonds, with two carbon atoms as points of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. The groups, −CH=CH−, −CH=C(CH_3)CH_2−, −CH=CHCH_2−, and , are non-limiting examples of alkenediyl groups. The term "substituted alkenediyl" refers to a non-aromatic divalent group, wherein the alkenediyl group is attached with two σ-bonds, with two carbon atoms as points of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The following groups are non-limiting examples of substituted alkenediyl groups: −CF=CH−, −C(OH)=CH−, and −CH_2CH=C(Cl)−.

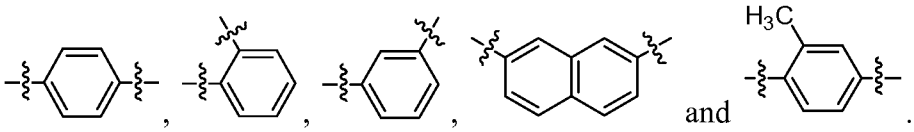
The term "alkynyl" when used without the "substituted" modifier refers to a monovalent group with a nonaromatic carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one carbon-carbon triple bond, and no atoms other than carbon and hydrogen. The groups, −C≡CH, −C≡CCH_3, −C≡CC_6H_5 and −CH_2C≡CCH_3, are non-limiting examples of alkynyl groups. The term "substituted alkynyl" refers to a monovalent group with a nonaromatic carbon atom as the point of attachment and at least one carbon-carbon triple bond, a linear or branched, cyclo, cyclic or acyclic structure, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The group, −C≡CSi(CH_3)$_3$, is a non-limiting example of a substituted alkynyl group.

The term "alkynediyl" when used without the "substituted" modifier refers to a non-aromatic divalent group, wherein the alkynediyl group is attached with two σ-bonds, with two carbon atoms as points of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one carbon-carbon triple bond, and no atoms other than carbon and

hydrogen. The groups, −C≡C−, −C≡CCH$_2$−, and −C≡CCH(CH$_3$)− are non-limiting examples of alkynediyl groups. The term "substituted alkynediyl" refers to a non-aromatic divalent group, wherein the alkynediyl group is attached with two σ-bonds, with two carbon atoms as points of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one carbon-carbon triple bond, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The groups −C≡CCFH− and −C≡CHCH(Cl)− are non-limiting examples of substituted alkynediyl groups.

The term "aryl" when used without the "substituted" modifier refers to a monovalent group with an aromatic carbon atom as the point of attachment, said carbon atom forming part of one or more six-membered aromatic ring structure(s) wherein the ring atoms are all carbon, and wherein the monovalent group consists of no atoms other than carbon and hydrogen. Non-limiting examples of aryl groups include phenyl (Ph), methylphenyl, (dimethyl)phenyl, −C$_6$H$_4$CH$_2$CH$_3$ (ethylphenyl), −C$_6$H$_4$CH$_2$CH$_2$CH$_3$ (propylphenyl), −C$_6$H$_4$CH(CH$_3$)$_2$, −C$_6$H$_4$CH(CH$_2$)$_2$, −C$_6$H$_3$(CH$_3$)CH$_2$CH$_3$ (methylethylphenyl), −C$_6$H$_4$CH=CH$_2$ (vinylphenyl), −C$_6$H$_4$CH=CHCH$_3$, −C$_6$H$_4$C≡CH, −C$_6$H$_4$C≡CCH$_3$, naphthyl, and the monovalent group derived from biphenyl. The term "substituted aryl" refers to a monovalent group with an aromatic carbon atom as the point of attachment, said carbon atom forming part of one or more six-membered aromatic ring structure(s) wherein the ring atoms are all carbon, and wherein the monovalent group further has at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. Non-limiting examples of substituted aryl groups include the groups: −C$_6$H$_4$F, −C$_6$H$_4$Cl, −C$_6$H$_4$Br, −C$_6$H$_4$I, −C$_6$H$_4$OH, −C$_6$H$_4$OCH$_3$, −C$_6$H$_4$OCH$_2$CH$_3$, −C$_6$H$_4$OC(O)CH$_3$, −C$_6$H$_4$NH$_2$, −C$_6$H$_4$NHCH$_3$, −C$_6$H$_4$N(CH$_3$)$_2$, −C$_6$H$_4$CH$_2$OH, −C$_6$H$_4$CH$_2$OC(O)CH$_3$, −C$_6$H$_4$CH$_2$NH$_2$, −C$_6$H$_4$CF$_3$, −C$_6$H$_4$CN, −C$_6$H$_4$CHO, −C$_6$H$_4$CHO, −C$_6$H$_4$C(O)CH$_3$, −C$_6$H$_4$C(O)C$_6$H$_5$, −C$_6$H$_4$CO$_2$H, −C$_6$H$_4$CO$_2$CH$_3$, −C$_6$H$_4$CONH$_2$, −C$_6$H$_4$CONHCH$_3$, and −C$_6$H$_4$CON(CH$_3$)$_2$.

The term "arenediyl" when used without the "substituted" modifier refers to a divalent group, wherein the arenediyl group is attached with two σ-bonds, with two aromatic carbon atoms as points of attachment, said carbon atoms forming part of one or more six-membered aromatic ring structure(s) wherein the ring atoms are all carbon, and wherein the monovalent group consists of no atoms other than carbon and hydrogen. Non-limiting examples of arenediyl groups include:



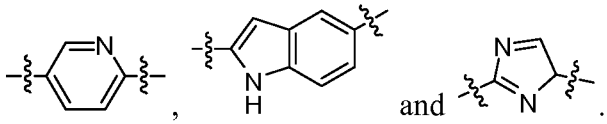
The term "substituted arenediyl" refers to a divalent group, wherein the arenediyl group is attached with two σ-bonds, with two aromatic carbon atoms as points of attachment, said carbon atoms forming part of one or more six-membered aromatic rings structure(s), wherein the ring atoms are carbon, and wherein the divalent group further has at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S.

The term "aralkyl" when used without the "substituted" modifier refers to the monovalent group −alkanediyl−aryl, in which the terms alkanediyl and aryl are each used in a manner consistent with the definitions provided above. Non-limiting examples of aralkyls are: phenylmethyl (benzyl, Bn), 1-phenyl-ethyl, 2-phenyl-ethyl, indenyl and 2,3-dihydro-indenyl, provided that indenyl and 2,3-dihydro-indenyl are only examples of aralkyl in so far as the point of attachment in each case is one of the saturated carbon atoms. When the term "aralkyl" is used with the "substituted" modifier, either one or both the alkanediyl and the aryl is substituted. Non-limiting examples of substituted aralkyls are: (3-chlorophenyl)-methyl, 2-oxo-2-phenyl-ethyl (phenylcarbonylmethyl), 2-chloro-2-phenyl-ethyl, chromanyl where the point of attachment is one of the saturated carbon atoms, and tetrahydroquinolinyl where the point of attachment is one of the saturated atoms.

The term "heteroaryl" when used without the "substituted" modifier refers to a monovalent group with an aromatic carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom forming part of an aromatic ring structure wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the monovalent group consists of no atoms other than carbon, hydrogen, aromatic nitrogen, aromatic oxygen and aromatic sulfur. Non-limiting examples of aryl groups include acridinyl, furanyl, imidazoimidazolyl, imidazopyrazolyl, imidazopyridinyl, imidazopyrimidinyl, indolyl, indazolinyl, methylpyridyl, oxazolyl, phenylimidazolyl, pyridyl, pyrrolyl, pyrimidyl, pyrazinyl, quinolyl, quinazolyl, quinoxalinyl, tetrahydroquinolinyl, thienyl, triazinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrrolopyrazinyl, pyrrolotriazinyl, pyrroloimidazolyl, chromenyl (where the point of attachment is one of the aromatic atoms), and chromanyl (where the point of attachment is one of the aromatic atoms). The term "substituted heteroaryl" refers to a monovalent group with an aromatic carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom forming part of an aromatic ring structure wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the monovalent group further has at least one atom independently selected from the group

consisting of non-aromatic nitrogen, non-aromatic oxygen, non aromatic sulfur F, Cl, Br, I, Si, and P.

The term "heteroarenediyl" when used without the "substituted" modifier refers to a divalent group, wherein the heteroarenediyl group is attached with two σ-bonds, with two atoms, aromatic carbon atom and/or aromatic nitrogen, as the point of attachment, said carbon atom or nitrogen atom forming part of one or more aromatic ring structure(s) wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the divalent group consists of no atoms other than carbon, hydrogen, aromatic nitrogen, aromatic oxygen and aromatic sulfur. Non-limiting examples of heteroarenediyl groups include:



The term "substituted heteroarenediyl" refers to a divalent group, wherein the heteroarenediyl group is attached with two σ-bonds, with an aromatic carbon atom or nitrogen atom as points of attachment, said carbon atom or nitrogen atom forming part of one or more six-membered aromatic ring structure(s), wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the divalent group further has at least one atom independently selected from the group consisting of non-aromatic nitrogen, non-aromatic oxygen, non aromatic sulfur F, Cl, Br, I, Si, and P.

The term "heteroaralkyl" when used without the "substituted" modifier refers to the monovalent group −alkanediyl−heteroaryl, in which the terms alkanediyl and heteroaryl are each used in a manner consistent with the definitions provided above. Non-limiting examples of aralkyls are: pyridylmethyl, and thienylmethyl. When the term "heteroaralkyl" is used with the "substituted" modifier, either one or both the alkanediyl and the heteroaryl is substituted.

The term "acyl" when used without the "substituted" modifier refers to a monovalent group with a carbon atom of a carbonyl group as the point of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure, further having no additional atoms that are not carbon or hydrogen, beyond the oxygen atom of the carbonyl group. The groups, −CHO, $-C(O)CH_3$ (acetyl, Ac), $-C(O)CH_2CH_3$, $-C(O)CH_2CH_2CH_3$, $-C(O)CH(CH_3)_2$, $-C(O)CH(CH_2)_2$, $-C(O)C_6H_5$, $-C(O)C_6H_4CH_3$, $-C(O)C_6H_4CH_2CH_3$, $-COC_6H_3(CH_3)_2$, and $-C(O)CH_2C_6H_5$, are non-limiting examples of acyl groups. The term "acyl" therefore encompasses, but is not limited to groups sometimes referred to as "alkyl carbonyl" and "aryl carbonyl" groups. The term "substituted acyl" refers to a monovalent group with a carbon

atom of a carbonyl group as the point of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure, further having at least one atom, in addition to the oxygen of the carbonyl group, independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The groups, $-C(O)CH_2CF_3$, $-CO_2H$ (carboxyl), $-CO_2CH_3$ (methylcarboxyl), $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$, $-CO_2C_6H_5$, $-CO_2CH(CH_3)_2$, $-CO_2CH(CH_2)_2$, $-C(O)NH_2$ (carbamoyl), $-C(O)NHCH_3$, $-C(O)NHCH_2CH_3$, $-CONHCH(CH_3)_2$, $-CONHCH(CH_2)_2$, $-CON(CH_3)_2$, $-CONHCH_2CF_3$, $-CO-$pyridyl, $-CO-$imidazoyl, and $-C(O)N_3$, are non-limiting examples of substituted acyl groups. The term "substituted acyl" encompasses, but is not limited to, "heteroaryl carbonyl" groups.

The term "alkylidene" when used without the "substituted" modifier refers to the divalent group =CRR′, wherein the alkylidene group is attached with one σ-bond and one π-bond, in which R and R′ are independently hydrogen, alkyl, or R and R′ are taken together to represent alkanediyl. Non-limiting examples of alkylidene groups include: $=CH_2$, $=CH(CH_2CH_3)$, and $=C(CH_3)_2$. The term "substituted alkylidene" refers to the group =CRR′, wherein the alkylidene group is attached with one σ-bond and one π-bond, in which R and R′ are independently hydrogen, alkyl, substituted alkyl, or R and R′ are taken together to represent a substituted alkanediyl, provided that either one of R and R′ is a substituted alkyl or R and R′ are taken together to represent a substituted alkanediyl.

The term "alkoxy" when used without the "substituted" modifier refers to the group $-OR$, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkoxy groups include: $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$, $-OCH(CH_2)_2$, $-O-$cyclopentyl, and $-O-$cyclohexyl. The term "substituted alkoxy" refers to the group $-OR$, in which R is a substituted alkyl, as that term is defined above. For example, $-OCH_2CF_3$ is a substituted alkoxy group.

The term "alkoxydiyl" when used without the "substituted" modifier refers to a non-aromatic divalent group, wherein the alkoxydiyl group is attached with two σ-bonds, with (a) two saturated carbon atoms as points of attachment, (b) one saturated carbon atom and one oxygen atom as points of attachment, or (c) two oxygen atoms as points of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds in the group's backbone, further having no backbone atoms other than carbon or oxygen and having at least one of each of these atoms in the group's backbone, and no side chains comprising groups other than hydrogen or alkyl. The groups, $-O-CH_2CH_2-$, $-CH_2-O-CH_2CH_2-$, $-O-CH_2CH_2-O-$ and $-O-CH_2-O-$ are non-limiting examples of

alkoxydiyl groups. The term "substituted alkanyloxydiyl" refers to a divalent group that is attached with two σ-bonds, with (a) two saturated carbon atoms as points of attachment, (b) one saturated carbon atom and one oxygen atom as points of attachment, or (c) two oxygen atoms as points of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and at least one atom independently selected from the group consisting of N, F, Cl, Br, I, Si, P, and S, or having additional oxygen atoms beyond those in the group's backbone. The following groups are non-limiting example of a substituted alkoxydiyl groups: $-O-CH_2C(OH)H-O-$ and $-O-CH_2C(Cl)H-O-$.

The terms "alkenyloxy", "alkynyloxy", "aryloxy", "aralkoxy", "heteroaryloxy", "heteroaralkoxy" and "acyloxy", when used without the "substituted" modifier, refers to groups, defined as −OR, in which R is alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively, as those terms are defined above. When any of the terms alkenyloxy, alkynyloxy, aryloxy, aralkyloxy and acyloxy is modified by "substituted," it refers to the group −OR, in which R is substituted alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively.

The term "alkenyloxydiyl" when used without the "substituted" modifier refers to a divalent group that is nonaromatic prior to attachment, wherein the alkenyloxydiyl group is attached with two σ-bonds, which may become aromatic upon attachment, with (a) two carbon atoms as points of attachment, (b) one carbon atom and one oxygen atom as points of attachment, or (c) two oxygen atoms as points of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure, at least one carbon-carbon double bond that is non-aromatic at least prior to attachment, further having no backbone atoms other than carbon or oxygen and having at least one of each of these atoms in the group's backbone, and no side chains comprising groups other than hydrogen or alkyl. The groups, $-O-CH=CH-$, $-O-CH=CHO-$ and $-O-CH=CHCH_2-$ are non-limiting examples of alkenyloxydiyl groups. The term "substituted alkenyloxydiyl" refers to a divalent group that is nonaromatic prior to attachment, wherein the substituted alkenyloxydiyl group is attached with two σ-bonds, which may become aromatic upon attachment, with (a) two carbon atoms as points of attachment, (b) one carbon atom and one oxygen atom as points of attachment, or (c) two oxygen atoms as points of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure, at least one carbon-carbon double bond that is non-aromatic at least prior to attachment and at least one atom independently selected from the group consisting of N, F, Cl, Br, I, Si, P, and S, or having additional oxygen atoms beyond those in the group's

backbone. The following groups are non-limiting example of a substituted alkenyloxydiyl groups: −O−CH=C(OH)−O− and −O−CH=C(Cl)−O−.

The term "alkylamino" when used without the "substituted" modifier refers to the group −NHR, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkylamino groups include: $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-NHCH(CH_3)_2$, $-NHCH(CH_2)_2$, $-NHCH_2CH_2CH_2CH_3$, $-NHCH(CH_3)CH_2CH_3$, $-NHCH_2CH(CH_3)_2$, $-NHC(CH_3)_3$, −NH−cyclopentyl, and −NH−cyclohexyl. The term "substituted alkylamino" refers to the group −NHR, in which R is a substituted alkyl, as that term is defined above. For example, $-NHCH_2CF_3$ is a substituted alkylamino group.

The term "dialkylamino" when used without the "substituted" modifier refers to the group −NRR′, in which R and R′ can be the same or different alkyl groups, or R and R′ can be taken together to represent an alkanediyl having two or more saturated carbon atoms, at least two of which are attached to the nitrogen atom. Non-limiting examples of dialkylamino groups include: $-NHC(CH_3)_3$, $-N(CH_3)CH_2CH_3$, $-N(CH_2CH_3)_2$, *N*-pyrrolidinyl, and *N*-piperidinyl. The term "substituted dialkylamino" refers to the group −NRR′, in which R and R′ can be the same or different substituted alkyl groups, one of R or R′ is an alkyl and the other is a substituted alkyl, or R and R′ can be taken together to represent a substituted alkanediyl with two or more saturated carbon atoms, at least two of which are attached to the nitrogen atom.

The terms "alkoxyamino", "alkenylamino", "alkynylamino", "arylamino", "aralkylamino", "heteroarylamino", "heteroaralkylamino", and "alkylsulfonylamino" when used without the "substituted" modifier, refers to groups, defined as −NHR, in which R is alkoxy, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and alkylsulfonyl, respectively, as those terms are defined above. A non-limiting example of an arylamino group is $-NHC_6H_5$. When any of the terms alkoxyamino, alkenylamino, alkynylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino and alkylsulfonylamino is modified by "substituted," it refers to the group −NHR, in which R is substituted alkoxy, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and alkylsulfonyl, respectively.

The term "amido" (acylamino), when used without the "substituted" modifier, refers to the group −NHR, in which R is acyl, as that term is defined above. A non-limiting example of an acylamino group is $-NHC(O)CH_3$. When the term amido is used with the "substituted" modifier, it refers to groups, defined as −NHR, in which R is substituted acyl, as that term is defined above. The groups $-NHC(O)OCH_3$ and $-NHC(O)NHCH_3$ are non-limiting examples of substituted amido groups.

The term "alkylaminodiyl" when used without the "substituted" modifier refers to a non-aromatic divalent group, wherein the alkylaminodiyl group is attached with two σ-bonds, with (a) two saturated carbon atoms as points of attachment, (b) one saturated carbon atom and one nitrogen atom as points of attachment, or (c) two nitrogen atoms as points of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure, no double or triple bonds in the group's backbone, further having no backbone atoms other than carbon or nitrogen and having at least one of each of these atoms in the group's backbone, and no side chains comprising groups other than hydrogen or alkyl. The groups, $-NH-CH_2CH_2-$, $-CH_2-NH-CH_2CH_2-$, $-NH-CH_2CH_2-NH-$ and $-NH-CH_2-NH-$ are non-limiting examples of alkylaminodiyl groups. The term "substituted alkylaminodiyl" refers to a divalent group, wherein the substituted alkylaminodiyl group is attached with two σ-bonds, with (a) two saturated carbon atoms as points of attachment, (b) one saturated carbon atom and one nitrogen atom as points of attachment, or (c) two nitrogen atoms as points of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds in the group's backbone, and at least one atom independently selected from the group consisting of O, F, Cl, Br, I, Si, P, and S, or having additional nitrogen atom beyond those in the group's backbone. The following groups are non-limiting example of a substituted alkylaminodiyl groups: $-NH-CH_2C(OH)H-NH-$ and $-NH-CH_2C(Cl)H-CH_2-$.

The term "alkenylaminodiyl" when used without the "substituted" modifier refers to a divalent group that is nonaromatic prior to attachment, wherein the alkenylaminodiyl group is attached with two σ-bonds, which may become aromatic upon attachment, with (a) two carbon atoms as points of attachment, (b) one carbon atom and one nitrogen atom as points of attachment, or (c) two nitrogen atoms as points of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure, at least one carbon-carbon double bond or carbon-nitrogen double that is non-aromatic at least prior to attachment, further having no backbone atoms other than carbon or nitrogen, and no side chains comprising groups other than hydrogen or alkyl. The groups, $-NH-CH=CH-$, $-NH-CH=N-$ and $-NH-CH=CH-NH-$ are non-limiting examples of alkenylaminodiyl groups. The term "substituted alkenylaminodiyl" refers to a divalent group that is nonaromatic prior to attachment, wherein the substituted alkenylaminodiyl group is attached with two σ-bonds, which may become aromatic upon attachment, with (a) two carbon atoms as points of attachment, (b) one carbon atom and one nitrogen atom as points of attachment, or (c) two nitrogen atoms as points of attachment, further having a linear or branched, cyclo, cyclic or

acyclic structure, at least one carbon-carbon double bond or carbon nitrogen double bond that is non-aromatic at least prior to attachment and at least one atom independently selected from the group consisting of O, F, Cl, Br, I, Si, P, and S, or having additional nitrogen atoms beyond those in the group's backbone. The following groups are non-limiting example of a substituted alkenylaminodiyl groups: −NH−CH=C(OH)−CH_2− and −N=CHC(Cl)H−.

The term "alkenylaminooxydiyl" when used without the "substituted" modifier refers to a divalent group, wherein the alkenylaminooxydiyl group is attached with two σ-bonds, which may become aromatic upon attachment, with two atoms selected from the group consisting of carbon, oxygen and nitrogen as points of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure, at least one carbon-carbon double bond, carbon-nitrogen double, or nitrogen-nitrogen double bond that is non-aromatic at least prior to attachment, further having no backbone atoms other than carbon nitrogen or oxygen and having at least one of each of these three atoms in the backbone, and no side chains comprising groups other than hydrogen or alkyl. The group −O−CH=N−, is a non-limiting example of an alkenylaminooxydiyl group. The term "substituted alkenylaminooxydiyl" refers to a divalent group that is attached with two σ-bonds, which may become aromatic upon attachment with two atoms selected from the group consisting of carbon, oxygen and nitrogen as points of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure, at least one carbon-carbon double bond or carbon nitrogen double bond that is non-aromatic at least prior to attachment and at least one atom independently selected from the group consisting of F, Cl, Br, I, Si, P, and S, or having one or more additional nitrogen and/or oxygen atoms beyond those in the group's backbone. The following groups are non-limiting example of a substituted alkenylaminooxydiyl groups: −NH−CH=C(OH)−O− and −N=CHC(Cl)H−O−.

The term "alkylimino" when used without the "substituted" modifier refers to the group =NR, wherein the alkylimino group is attached with one σ-bond and one π-bond, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkylimino groups include: =NCH_3, =NCH_2CH_3 and =N−cyclohexyl. The term "substituted alkylimino" refers to the group =NR, wherein the alkylimino group is attached with one σ-bond and one π-bond, in which R is a substituted alkyl, as that term is defined above. For example, =NCH_2CF_3 is a substituted alkylimino group.

Similarly, the terms "alkenylimino", "alkynylimino", "arylimino", "aralkylimino", "heteroarylimino", "heteroaralkylimino" and "acylimino", when used without the

"substituted" modifier, refers to groups, defined as =NR, wherein the alkylimino group is attached with one σ-bond and one π-bond, in which R is alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively, as those terms are defined above. When any of the terms alkenylimino, alkynylimino, arylimino, aralkylimino and acylimino is modified by "substituted," it refers to the group =NR, wherein the alkylimino group is attached with one σ-bond and one π-bond, in which R is substituted alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively.

The term "fluoroalkyl" when used without the "substituted" modifier refers to an alkyl, as that term is defined above, in which one or more fluorines have been substituted for hydrogens. The groups, $-CH_2F$, $-CF_2H$, $-CF_3$, and $-CH_2CF_3$ are non-limiting examples of fluoroalkyl groups. The term "substituted fluoroalkyl" refers to a non-aromatic monovalent group with a saturated carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one fluorine atom, no carbon-carbon double or triple bonds, and at least one atom independently selected from the group consisting of N, O, Cl, Br, I, Si, P, and S. The following group is a non-limiting example of a substituted fluoroalkyl: −CFHOH.

The term "alkylphosphate" when used without the "substituted" modifier refers to the group −OP(O)(OH)(OR), in which R is an alkyl, as that term is defined above. Non-limiting examples of alkylphosphate groups include: −OP(O)(OH)(OMe) and −OP(O)(OH)(OEt). The term "substituted alkylphosphate" refers to the group −OP(O)(OH)(OR), in which R is a substituted alkyl, as that term is defined above.

The term "dialkylphosphate" when used without the "substituted" modifier refers to the group −OP(O)(OR)(OR′), in which R and R′ can be the same or different alkyl groups, or R and R′ can be taken together to represent an alkanediyl having two or more saturated carbon atoms, at least two of which are attached via the oxygen atoms to the phosphorus atom. Non-limiting examples of dialkylphosphate groups include: $-OP(O)(OMe)_2$, −OP(O)(OEt)(OMe) and $-OP(O)(OEt)_2$. The term "substituted dialkylphosphate" refers to the group −OP(O)(OR)(OR′), in which R and R′ can be the same or different substituted alkyl groups, one of R or R′ is an alkyl and the other is a substituted alkyl, or R and R′ can be taken together to represent a substituted alkanediyl with two or more saturated carbon atoms, at least two of which are attached via the oxygen atoms to the phosphorous.

The term "alkylthio" when used without the "substituted" modifier refers to the group −SR, in which R is an alkyl, as that term is defined above. Non-limiting examples of

alkylthio groups include: $-SCH_3$, $-SCH_2CH_3$, $-SCH_2CH_2CH_3$, $-SCH(CH_3)_2$, $-SCH(CH_2)_2$, −S−cyclopentyl, and −S−cyclohexyl. The term "substituted alkylthio" refers to the group −SR, in which R is a substituted alkyl, as that term is defined above. For example, $-SCH_2CF_3$ is a substituted alkylthio group.

Similarly, the terms "alkenylthio", "alkynylthio", "arylthio", "aralkylthio", "heteroarylthio", "heteroaralkylthio", and "acylthio", when used without the "substituted" modifier, refers to groups, defined as −SR, in which R is alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively, as those terms are defined above. When any of the terms alkenylthio, alkynylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, and acylthio is modified by "substituted," it refers to the group −SR, in which R is substituted alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively.

The term "thioacyl" when used without the "substituted" modifier refers to a monovalent group with a carbon atom of a thiocarbonyl group as the point of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure, further having no additional atoms that are not carbon or hydrogen, beyond the sulfur atom of the carbonyl group. The groups, −CHS, $-C(S)CH_3$, $-C(S)CH_2CH_3$, $-C(S)CH_2CH_2CH_3$, $-C(S)CH(CH_3)_2$, $-C(S)CH(CH_2)_2$, $-C(S)C_6H_5$, $-C(S)C_6H_4CH_3$, $-C(S)C_6H_4CH_2CH_3$, $-C(S)C_6H_3(CH_3)_2$, and $-C(S)CH_2C_6H_5$, are non-limiting examples of thioacyl groups. The term "thioacyl" therefore encompasses, but is not limited to, groups sometimes referred to as "alkyl thiocarbonyl" and "aryl thiocarbonyl" groups. The term "substituted thioacyl" refers to a radical with a carbon atom as the point of attachment, the carbon atom being part of a thiocarbonyl group, further having a linear or branched, cyclo, cyclic or acyclic structure, further having at least one atom, in addition to the sulfur atom of the carbonyl group, independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The groups, $-C(S)CH_2CF_3$, $-C(S)O_2H$, $-C(S)OCH_3$, $-C(S)OCH_2CH_3$, $-C(S)OCH_2CH_2CH_3$, $-C(S)OC_6H_5$, $-C(S)OCH(CH_3)_2$, $-C(S)OCH(CH_2)_2$, $-C(S)NH_2$, and $-C(S)NHCH_3$, are non-limiting examples of substituted thioacyl groups. The term "substituted thioacyl" encompasses, but is not limited to, "heteroaryl thiocarbonyl" groups.

The term "alkylsulfonyl" when used without the "substituted" modifier refers to the group $-S(O)_2R$, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkylsulfonyl groups include: $-S(O)_2CH_3$, $-S(O)_2CH_2CH_3$, $-S(O)_2CH_2CH_2CH_3$, $-S(O)_2CH(CH_3)_2$, $-S(O)_2CH(CH_2)_2$, $-S(O)_2$−cyclopentyl, and $-S(O)_2$−cyclohexyl. The term "substituted alkylsulfonyl" refers to the group $-S(O)_2R$, in which R is a substituted alkyl, as that term is defined above. For example, $-S(O)_2CH_2CF_3$ is a substituted alkylsulfonyl group.

Similarly, the terms "alkenylsulfonyl", "alkynylsulfonyl", "arylsulfonyl", "aralkylsulfonyl", "heteroarylsulfonyl", and "heteroaralkylsulfonyl" when used without the "substituted" modifier, refers to groups, defined as $-S(O)_2R$, in which R is alkenyl, alkynyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, respectively, as those terms are defined above. When any of the terms alkenylsulfonyl, alkynylsulfonyl, arylsulfonyl, aralkylsulfonyl, heteroarylsulfonyl, and heteroaralkylsulfonyl is modified by "substituted," it refers to the group $-S(O)_2R$, in which R is substituted alkenyl, alkynyl, aryl, aralkyl, heteroaryl and heteroaralkyl, respectively.

The term "alkylsulfinyl" when used without the "substituted" modifier refers to the group $-S(O)R$, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkylsulfinyl groups include: $-S(O)CH_3$, $-S(O)CH_2CH_3$, $-S(O)CH_2CH_2CH_3$, $-S(O)CH(CH_3)_2$, $-S(O)CH(CH_2)_2$, $-S(O)$−cyclopentyl, and $-S(O)$−cyclohexyl. The term "substituted alkylsulfinyl" refers to the group $-S(O)R$, in which R is a substituted alkyl, as that term is defined above. For example, $-S(O)CH_2CF_3$ is a substituted alkylsulfinyl group.

Similarly, the terms "alkenylsulfinyl", "alkynylsulfinyl", "arylsulfinyl", "aralkylsulfinyl", "heteroarylsulfinyl", and "heteroaralkylsulfinyl" when used without the "substituted" modifier, refers to groups, defined as $-S(O)R$, in which R is alkenyl, alkynyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, respectively, as those terms are defined above. When any of the terms alkenylsulfinyl, alkynylsulfinyl, arylsulfinyl, aralkylsulfinyl, heteroarylsulfinyl, and heteroaralkylsulfinyl is modified by "substituted," it refers to the group $-S(O)R$, in which R is substituted alkenyl, alkynyl, aryl, aralkyl, heteroaryl and heteroaralkyl, respectively.

The term "alkylsilyl" when used without the "substituted" modifier refers to a monovalent group, defined as $-SiH_2R$, $-SiHRR'$, or $-SiRR'R''$, in which R, R′ and R″ can be the same or different alkyl groups, or any combination of two of R, R′ and R″ can be taken together to represent an alkanediyl. The groups, $-SiH_2CH_3$, $-SiH(CH_3)_2$, $-Si(CH_3)_3$ and $-Si(CH_3)_2C(CH_3)_3$, are non-limiting examples of unsubstituted alkylsilyl groups. The term "substituted alkylsilyl" refers to $-SiH_2R$, $-SiHRR'$, or $-SiRR'R''$, in which at least one of R, R′ and R″ is a substituted alkyl or two of R, R′ and R″ can be taken together to represent a substituted alkanediyl. When more than one of R, R′ and R″ is a substituted alkyl, they can be the same of different. Any of R, R′ and R″ that are not either substituted alkyl or substituted alkanediyl, can be either alkyl, either the same or different, or can be taken together to represent a alkanediyl with two or more saturated carbon atoms, at least two of which are attached to the silicon atom.

In addition, atoms making up the compounds of the present invention are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{13}C and ^{14}C. Similarly, it is contemplated that one or more carbon atom(s) of a compound of the present invention may be replaced by a silicon atom(s). Furthermore, it is contemplated that one or more oxygen atom(s) of a compound of the present invention may be replaced by a sulfur or selenium atom(s).

A single dashed line between two atoms indicates an optional bond. The bond may not be present at all, it may be present as a single bond, or it may be present as a double bound. If an atom is only connected to dashed lines, then the atom itself is optional. It may be present or it may not be present.

A bond shown as a combination of a solid and a dashed line indicates that the bond is either a single bond or a double bond. Thus, for example, the structure  includes the structures , , ,  and .

As will be understood by a person of skill in the art, no one such ring atom forms part of more than one double bond.

Any undefined valency on an atom of a structure shown in this application implicitly represents a hydrogen atom bonded to the atom.

As used herein, a "chiral auxiliary" refers to a removable chiral group that is capable of influencing the stereoselectivity of a reaction. Persons of skill in the art are familiar with such compounds, and many are commercially available.

The use of the word "a" or "an," when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one."

Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that

"comprises," "has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

The term "effective," as that term is used in the specification and/or claims, means adequate to accomplish a desired, expected, or intended result.

The term "hydrate" when used as a modifier to a compound means that the compound has less than one (*e.g.*, hemihydrate), one (*e.g.*, monohydrate), or more than one (*e.g.*, dihydrate) water molecules associated with each compound molecule, such as in solid forms of the compound.

As used herein, the term "IC_{50}" refers to an inhibitory dose which is 50% of the maximum response obtained.

An "isomer" of a first compound is a separate compound in which each molecule contains the same constituent atoms as the first compound, but where the configuration of those atoms in three dimensions differs.

As used herein, the term "patient" or "subject" refers to a living mammalian organism, such as a human, monkey, cow, sheep, goat, dog, cat, mouse, rat, guinea pig, or transgenic species thereof. In certain embodiments, the patient or subject is a primate. Non-limiting examples of human subjects are adults, juveniles, infants and fetuses.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts of compounds of the present invention which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, 2-naphthalenesulfonic acid, 3-phenylpropionic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, acetic acid, aliphatic mono- and dicarboxylic acids, aliphatic sulfuric acids, aromatic sulfuric acids, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclopentanepropionic acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, heptanoic acid, hexanoic acid, hydroxynaphthoic acid, lactic acid, laurylsulfuric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, muconic acid, *o*-(4-hydroxybenzoyl)benzoic acid,

oxalic acid, *p*-chlorobenzenesulfonic acid, phenyl-substituted alkanoic acids, propionic acid, *p*-toluenesulfonic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, tartaric acid, tertiarybutylacetic acid, trimethylacetic acid, and the like. Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like. It should be recognized that the particular anion or cation forming a part of any salt of this invention is not critical, so long as the salt, as a whole, is pharmacologically acceptable. Additional examples of pharmaceutically acceptable salts and their methods of preparation and use are presented in *Handbook of Pharmaceutical Salts: Properties, and Use* (2002).

As used herein, "predominantly one enantiomer" means that a compound contains at least about 85% of one enantiomer, or more preferably at least about 90% of one enantiomer, or even more preferably at least about 95% of one enantiomer, or most preferably at least about 99% of one enantiomer. Similarly, the phrase "substantially free from other optical isomers" means that the composition contains at most about 15% of another enantiomer or diastereomer, more preferably at most about 10% of another enantiomer or diastereomer, even more preferably at most about 5% of another enantiomer or diastereomer, and most preferably at most about 1% of another enantiomer or diastereomer.

"Prevention" or "preventing" includes: (1) inhibiting the onset of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease, and/or (2) slowing the onset of the pathology or symptomatology of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease.

"Prodrug" means a compound that is convertible *in vivo* metabolically into an inhibitor according to the present invention. The prodrug itself may or may not also have activity with respect to a given target protein. For example, a compound comprising a hydroxy group may be administered as an ester that is converted by hydrolysis *in vivo* to the hydroxy compound. Suitable esters that may be converted *in vivo* into hydroxy compounds include acetates, citrates, lactates, phosphates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoate, gentisates,

isethionates, di-*p*-toluoyltartrates, methanesulfonates, ethanesulfonates, benzenesulfonates, *p*-toluenesulfonates, cyclohexylsulfamates, quinates, esters of amino acids, and the like. Similarly, a compound comprising an amine group may be administered as an amide that is converted by hydrolysis *in vivo* to the amine compound.

A "repeat unit" is the simplest structural entity of certain materials, for example, frameworks and/or polymers, whether organic, inorganic or metal-organic. In the case of a polymer chain, repeat units are linked together successively along the chain, like the beads of a necklace. For example, in polyethylene, -[-CH_2CH_2-]$_n$-, the repeat unit is $-CH_2CH_2-$. The subscript "n" denotes the degree of polymerisation, that is, the number of repeat units linked together. When the value for "n" is left undefined, it simply designates repetition of the formula within the brackets as well as the polymeric nature of the material. The concept of a repeat unit applies equally to where the connectivity between the repeat units extends three dimensionally, such as in metal organic frameworks, cross-linked polymers, thermosetting polymers, etc.

The term "saturated" when referring to an atom means that the atom is connected to other atoms only by means of single bonds.

A "stereoisomer" or "optical isomer" is an isomer of a given compound in which the same atoms are bonded to the same other atoms, but where the configuration of those atoms in three dimensions differs. "Enantiomers" are stereoisomers of a given compound that are mirror images of each other, like left and right hands. "Diastereomers" are stereoisomers of a given compound that are not enantiomers.

The invention contemplates that for any stereocenter or axis of chirality for which stereochemistry has not been defined, that stereocenter or axis of chirality can be present in its *R* form, *S* form, or as a mixture of the *R* and *S* forms, including racemic and non-racemic mixtures.

"Substituent convertible to hydrogen *in vivo*" means any group that is convertible to a hydrogen atom by enzymological or chemical means including, but not limited to, hydrolysis and hydrogenolysis. Examples include hydrolyzable groups, such as acyl groups, groups having an oxycarbonyl group, amino acid residues, peptide residues, *o*-nitrophenylsulfenyl, trimethylsilyl, tetrahydro-pyranyl, diphenylphosphinyl, and the like. Examples of acyl groups include formyl, acetyl, trifluoroacetyl, and the like. Examples of groups having an oxycarbonyl group include ethoxycarbonyl, *tert*-butoxycarbonyl ($-C(O)OC(CH_3)_3$), benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, vinyloxycarbonyl, β-(*p*-toluenesulfonyl)ethoxycarbonyl, and the like. Suitable amino acid residues include, but are

not limited to, residues of Gly (glycine), Ala (alanine), Arg (arginine), Asn (asparagine), Asp (aspartic acid), Cys (cysteine), Glu (glutamic acid), His (histidine), Ile (isoleucine), Leu (leucine), Lys (lysine), Met (methionine), Phe (phenylalanine), Pro (proline), Ser (serine), Thr (threonine), Trp (tryptophan), Tyr (tyrosine), Val (valine), Nva (norvaline), Hse (homoserine), 4-Hyp (4-hydroxyproline), 5-Hyl (5-hydroxylysine), Orn (ornithine) and β-Ala. Examples of suitable amino acid residues also include amino acid residues that are protected with a protecting group. Examples of suitable protecting groups include those typically employed in peptide synthesis, including acyl groups (such as formyl and acetyl), arylmethyloxycarbonyl groups (such as benzyloxycarbonyl and p-nitrobenzyloxycarbonyl), *tert*-butoxycarbonyl groups ($-C(O)OC(CH_3)_3$), and the like. Suitable peptide residues include peptide residues comprising two to five, and optionally amino acid residues. The residues of these amino acids or peptides can be present in stereochemical configurations of the D-form, the L-form or mixtures thereof. In addition, the amino acid or peptide residue may have an asymmetric carbon atom. Examples of suitable amino acid residues having an asymmetric carbon atom include residues of Ala, Leu, Phe, Trp, Nva, Val, Met, Ser, Lys, Thr and Tyr. Peptide residues having an asymmetric carbon atom include peptide residues having one or more constituent amino acid residues having an asymmetric carbon atom. Examples of suitable amino acid protecting groups include those typically employed in peptide synthesis, including acyl groups (such as formyl and acetyl), arylmethyloxycarbonyl groups (such as benzyloxycarbonyl and *p*-nitrobenzyloxycarbonyl), *tert*-butoxycarbonyl groups ($-C(O)OC(CH_3)_3$), and the like. Other examples of substituents "convertible to hydrogen *in vivo*" include reductively eliminable hydrogenolyzable groups. Examples of suitable reductively eliminable hydrogenolyzable groups include, but are not limited to, arylsulfonyl groups (such as *o*-toluenesulfonyl); methyl groups substituted with phenyl or benzyloxy (such as benzyl, trityl and benzyloxymethyl); arylmethoxycarbonyl groups (such as benzyloxycarbonyl and o-methoxy-benzyloxycarbonyl); and haloethoxycarbonyl groups (such as β,β,β-trichloroethoxycarbonyl and β-iodoethoxycarbonyl).

"Therapeutically effective amount" or "pharmaceutically effective amount" means that amount which, when administered to a subject or patient for treating a disease, is sufficient to effect such treatment for the disease.

"Treatment" or "treating" includes (1) inhibiting a disease in a subject or patient experiencing or displaying the pathology or symptomatology of the disease (*e.g.*, arresting further development of the pathology and/or symptomatology), (2) ameliorating a disease in a subject or patient that is experiencing or displaying the pathology or symptomatology of the

disease (*e.g.*, reversing the pathology and/or symptomatology), and/or (3) effecting any measurable decrease in a disease in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease.

As used herein, the term "water soluble" means that the compound dissolves in water at least to the extent of 0.010 mole/liter or is classified as soluble according to literature precedence.

Other abbreviations used herein are as follows: DMSO, dimethyl sulfoxide; NO, nitric oxide; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; NGF, nerve growth factor; IBMX, isobutylmethylxanthine; FBS, fetal bovine serum; GPDH, glycerol 3-phosphate dehydrogenase; RXR, retinoid X receptor; TGF-β, transforming growth factor-β; IFNγ or IFN-γ, interferon-γ; LPS, bacterial endotoxic lipopolysaccharide; TNFα or TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; MTT, 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide; TCA, trichloroacetic acid; HO-1, inducible heme oxygenase.

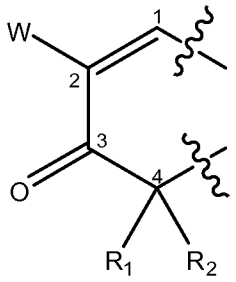
The above definitions supersede any conflicting definition in any of the reference that is incorporated by reference herein. The fact that certain terms are defined, however, should not be considered as indicative that any term that is undefined is indefinite. Rather, all terms used are believed to describe the invention in terms such that one of ordinary skill can appreciate the scope and practice the present invention.

IV. Compounds for the Treatment of Obesity

In one aspect of the present disclosure, there are provided methods of reducing weight in a patient in need thereof comprising administering to the subject an antioxidant inflammation modulator (AIM) in an amount sufficient to reduce the patient's weight. These compounds, and molecules containing similar structural features and pharmacology, are known as antioxidant inflammation modulators, or AIMs. A structural feature shared by AIMs is the presence of at least one substructure comprising an alpha, beta-unsaturated carbonyl group with a nitrile group, CF_3 group, or other electron-withdrawing group attached to the alpha carbon. These compounds have shown the ability to activate Nrf2, as measured by elevated expression of one or more Nrf2 target genes (*e.g.*, NQO1 or HO-1; Dinkova-Kostova *et al.*, 2005). Further, these compounds are capable of indirect and direct inhibition of pro-inflammatory transcription factors including NF-kappa B and STAT3 (Ahmad *et al.*, 2006; Ahmad *et al.,* 2008). In some aspects, there are provided methods of inhibiting a weight gene in a subject in need thereof comprising administering to the subject an

antioxidant inflammation modulator (AIM), including any of the specific compounds disclosed herein, in an amount sufficient to inhibit the weight gene in the subject. In some aspects, there are provided methods of preventing obesity in a subject in need thereof comprising administering to the subject an antioxidant inflammation modulator (AIM), including any of the specific compounds disclosed herein, in an amount sufficient to prevent obesity in the subject. In some aspects, there are provided methods of preventing progression of obesity in a subject in need thereof comprising administering to the subject an antioxidant inflammation modulator (AIM), including any of the specific compounds disclosed herein, in an amount sufficient to prevent progression of obesity in the subject.

In some embodiments, the AIM is a selective activator of the antioxidant transcription factor Nrf2. AIMs for use with this inventions may be represented by the following moiety:



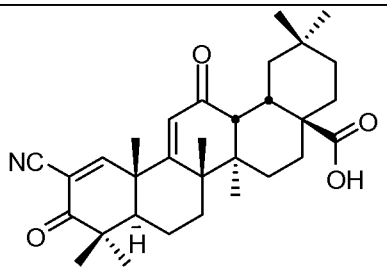
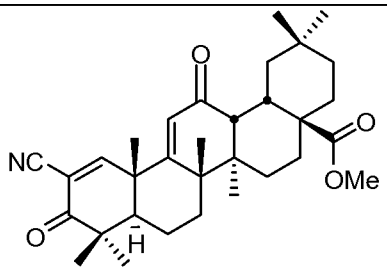
wherein W is nitrile, CF_3 or other electron-withdrawing group, and R_1 and R_2 are as defined above and in the claims below. This pharmacore is found in a variety of synthetic triterpenoids, such as those described by Honda *et al.* (2000a); Honda *et al.*, (2000b); Honda *et al.* (2002); and U.S. Patent Application Publications 2009/0326063, 2010/0056777, 2010/0048892, 2010/0048911 and 2010/0041904, each of which is incorporated herein by reference. This pharmacore is also found in a variety of other, non-triterpenoid compounds, for example, tricyclic bis-enones (*e.g.*, TBE-31) as embodied in US Patent Application Publications 2003/0232786 and 2008/0261985, both of which are incorporated by reference herein. Also this pharmacore is also disclosed in U.S. Patent Application Publication 2010/0048887, which is also incorporated by reference herein. Many of these compounds, both the triterpenoid and non-triterpenoid, are highly potent and selective activators of the antioxidant transcription factor Nrf2. Further many of these compounds have been tied to a variety of anti-inflammatory-related activities including, for example, anti-proliferative activities and/or antioxidant activities such as induction of heme oxygenase-1 (HO-1) *in vitro* and *in vivo*, induction of CD11b expression, inhibition of iNOS induction, inhibition of COX-2 induction, inhibition of NO production, induction of apoptosis in cancer cells, inhibition of

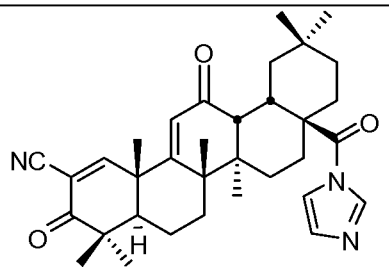
NF-κB, activation of the JNK pathway, and phase 2 induction (elevation of NAD(P)H-quinone oxidoreductase and HO-1). Induction of the Phase 2 response is related to activation of the transcription factor Nrf2, which has been shown to activate the antioxidant response element (ARE) in the promoter region of many antioxidant, anti-inflammatory, and cytoprotective genes, and Phase 2 activation is highly correlated with potent inhibition of NO production in activated macrophages (*e.g.*, Dinkova-Kostova *et al.*, 2005).

One AIM, bardoxolone methyl (BARD), is in advanced clinical trials for the treatment of chronic kidney disease. Data from these and other clinical trials have shown that BARD induces Nrf2 activity in blood cells at therapeutic doses. In the course of these studies the current inventors have identified a clinical scenario in which, following treatment with bardoxolone methyl, overweight or obese patients exhibit a reduction in weight (Table 1).

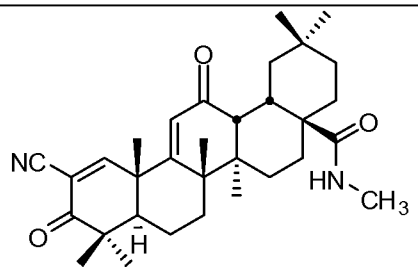
In certain embodiments, compounds amenable to modification with the above pharmacore include, but are not limited to, triterpenoids (non-limiting examples include argentatin, betulinic acid, lanostane, oleanic acid, ursolic acid, glycyrrhetinic acid, boswellic acid, faradiol, calenduladiol, and moronic acid), saponins (*e.g.*, ginsenoside), avicins, resveratrol, curcumin, gossypol, epigallocatechin, epigallocatechin-3-gallate (EGCG), gossypol, lapachol, other flavonoids (non-limiting examples include quercetin, daidzein, luteolin, coumarin, wogonin and baicalin), dehydroandrosterone (DHEA), cholic acid, deoxycholic acid, ginsenoside (*e.g.*, 20(*S*)-ginsenoside), silymarin, anthocyanins, avenanthramides, cucurbitacins, aloesin, aloe-emodin, and/or tubeimosides.

Non-limiting examples of triterpenoids that may be used in accordance with the methods of this invention are shown here.

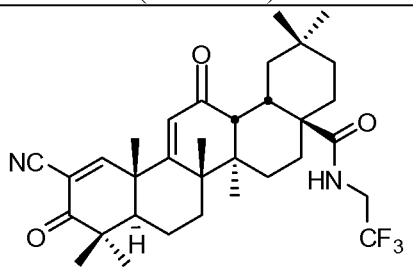
 CDDO (TP-151) (RTA 401)	 bardoxolone methyl (BARD) CDDO-Me (TP-155) (RTA 402)



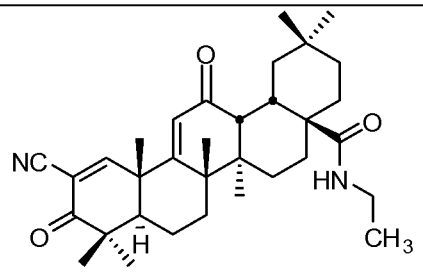
CDDO-Im
(TP-235)
(RTA 403)



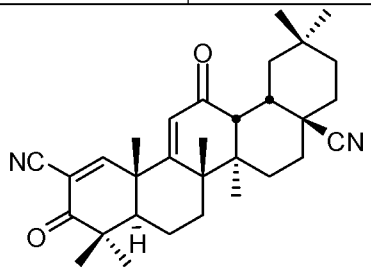
CDDO-MA
(TP-224)



CDDP-TFEA
(TP-500)
(RTA 404)

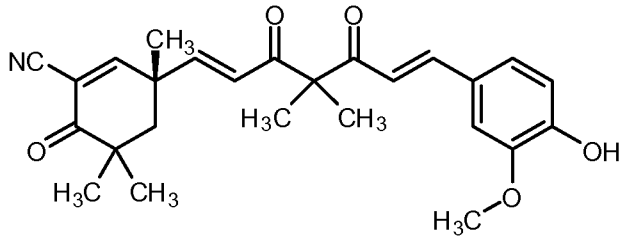


CDDO-EA
(TP-319)
(RTA 405)

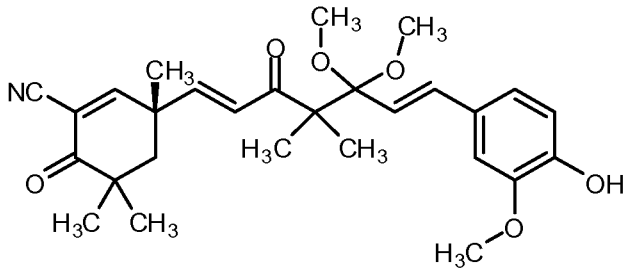


TP-225

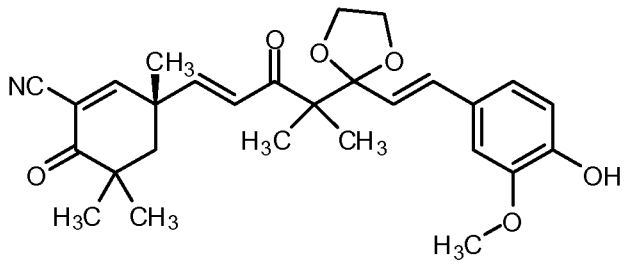
Non-limiting examples of non-triterpenoid compounds that may be used in accordance with the methods of this invention are shown here.



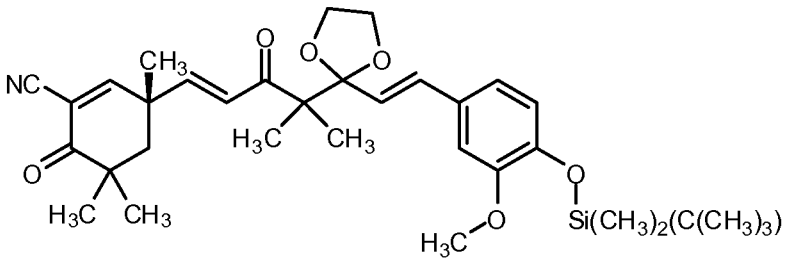
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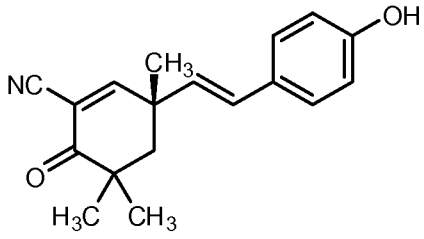
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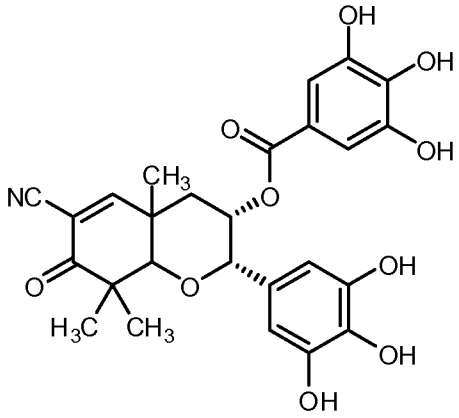
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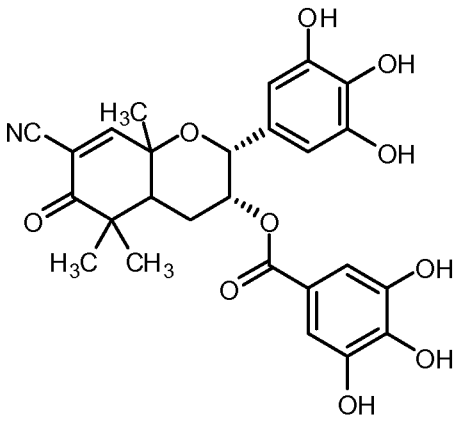
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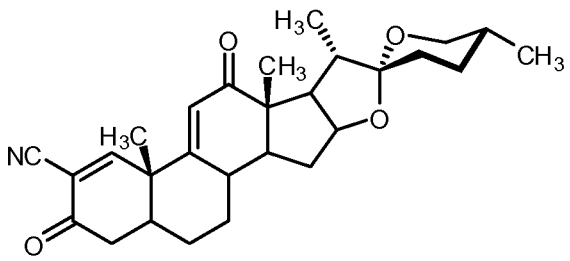
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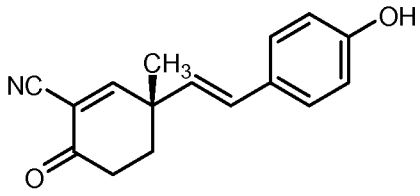
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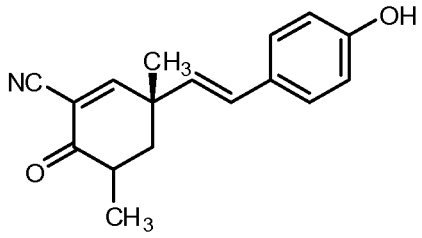
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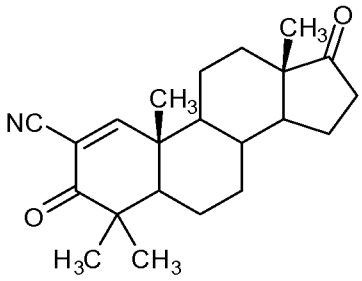
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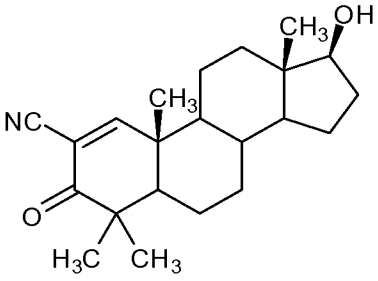
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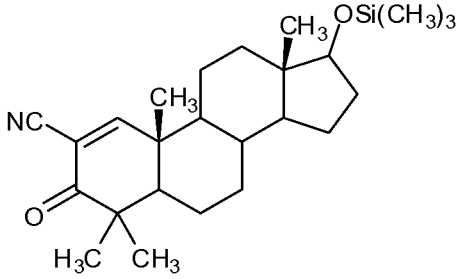
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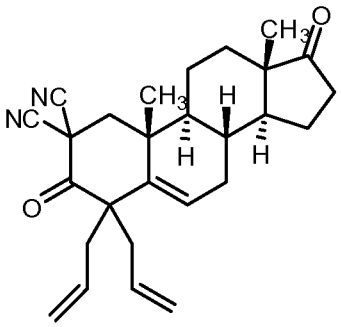
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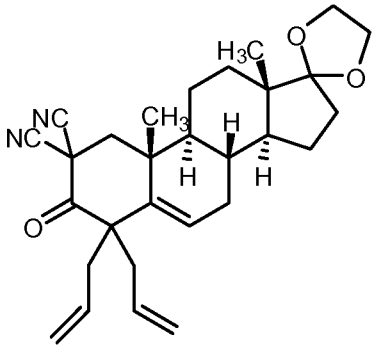
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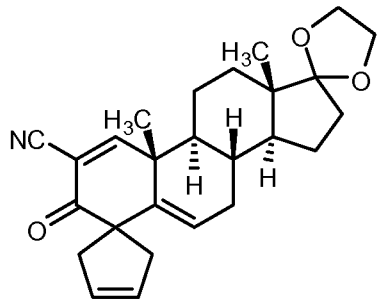
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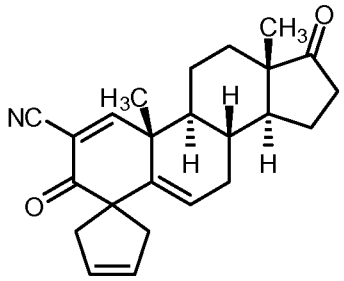
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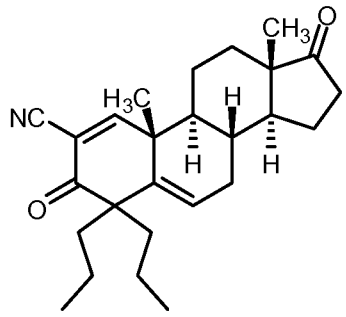
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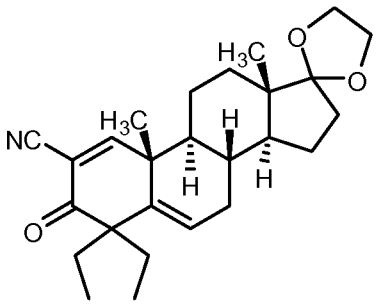
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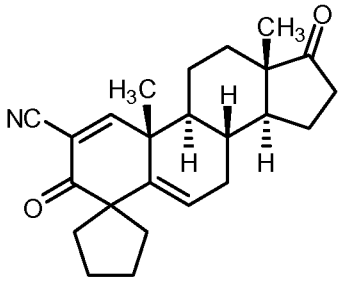
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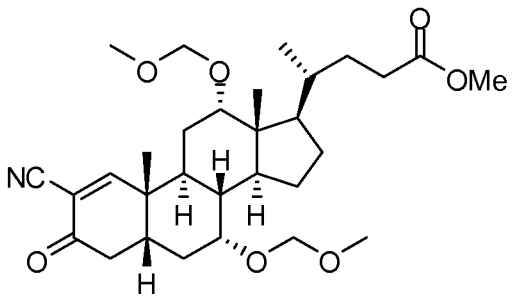
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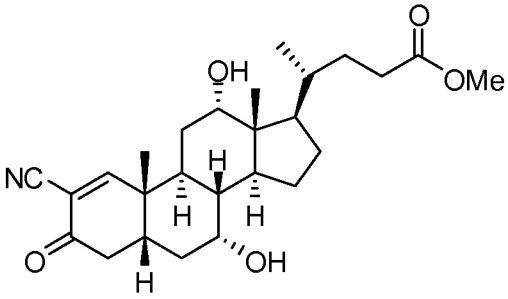
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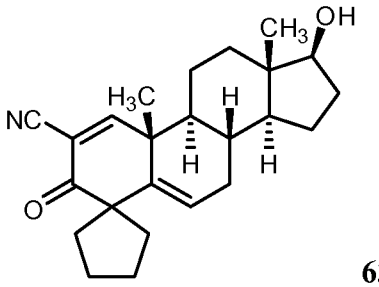
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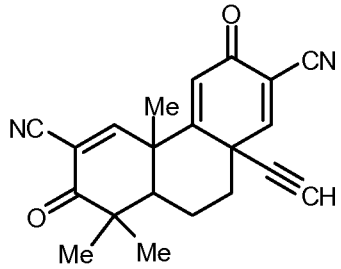
63312



63314



63329



TBE-31

Although some of the most potent and selective known activators of Nrf2 are AIMs, compounds based on other molecular scaffolds have also been reported to activate Nrf2. These include sulforaphane, oltipraz, dimethyl fumarate, statins, cyclopentenone

prostaglandins, and NO-donating molecules (*see, e.g.*, Yates *et al.*, 2006; 2009; Habeos *et al.*, 2008; Nguyen *et al.*, 2009; Kansanen *et al.,* 2009; Kobayashi *et al.,* 2009; Gao *et al.,* 2006).

Compounds employed in may be made using the methods described by Honda *et al.* (2000a); Honda *et al.*, (2000b); Honda *et al.* (2002); and U.S. Patent Application Publications 2009/0326063, 2010/0056777, 2010/0048892, 2010/0048911, 2010/0041904, 2003/0232786, 2008/0261985 and 2010/0048887, all of which are incorporated by reference herein. These methods can be further modified and optimized using the principles and techniques of organic chemistry as applied by a person skilled in the art. Such principles and techniques are taught, for example, in *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (2007), which is also incorporated by reference herein.

Compounds employed in methods of the invention may contain one or more asymmetrically-substituted carbon or nitrogen atoms, and may be isolated in optically active or racemic form. Thus, all chiral, diastereomeric, racemic form, epimeric form, and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. Compounds may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. In some embodiments, a single diastereomer is obtained. The chiral centers of the compounds of the present invention can have the *S* or the *R* configuration.

Polymorphic forms of the compounds of the present invention, *e.g.*, Forms A and B of CDDO-Me, may be used in accordance with the methods of this inventions. Form B displays a bioavailability that is surprisingly better than that of Form A. Specifically the bioavailability of Form B was higher than that of Form A CDDO-Me in monkeys when the monkeys received equivalent dosages of the two forms orally, in gelatin capsules. See U.S. Patent Application Publication 2009/0048204, which is incorporated by reference herein in its entirety.

"Form A" of CDDO-Me (RTA 402) is unsolvated (non-hydrous) and can be characterized by a distinctive crystal structure, with a space group of $P4_3\,2_12$ (no. 96) unit cell dimensions of a = 14.2 Å, b = 14.2 Å and c = 81.6 Å, and by a packing structure, whereby three molecules are packed in helical fashion down the crystallographic *b* axis. In some embodiments, Form A can also be characterized by X-ray powder diffraction (XRPD) pattern (CuKα) comprising significant diffraction peaks at about 8.8, 12.9, 13.4, 14.2 and 17.4 $^{o}2\theta$. In some variations, the X-ray powder diffraction of Form A is substantially as shown in FIG. 1A or FIG. 1B.

Unlike Form A, "Form B" of CDDO-Me is in a single phase but lacks such a defined crystal structure. Samples of Form B show no long-range molecular correlation, *i.e.*, above roughly 20 Å. Moreover, thermal analysis of Form B samples reveals a glass transition temperature (T_g) in a range from about 120 °C to about 130 °C. In contrast, a disordered nanocrystalline material does not display a T_g but instead only a melting temperature (T_m), above which crystalline structure becomes a liquid. Form B is typified by an XRPD spectrum (FIG 1C) differing from that of Form A (FIG. 1A or FIG. 1B). Since it does not have a defined crystal structure, Form B likewise lacks distinct XRPD peaks, such as those that typify Form A, and instead is characterized by a general "halo" XRPD pattern. In particular, the non-crystalline Form B falls into the category of "X-ray amorphous" solids because its XRPD pattern exhibits three or fewer primary diffraction halos. Within this category, Form B is a "glassy" material.

Form A and Form B of CDDO-Me are readily prepared from a variety of solutions of the compound. For example, Form B can be prepared by fast evaporation or slow evaporation in MTBE, THF, toluene, or ethyl acetate. Form A can be prepared in several ways, including via fast evaporation, slow evaporation, or slow cooling of a CDDO-Me solution in ethanol or methanol. Preparations of CDDO-Me in acetone can produce either Form A, using fast evaporation, or Form B, using slow evaporation.

Various means of characterization can be used together to distinguish Form A and Form B CDDO-Me from each other and from other forms of CDDO-Me. Illustrative of the techniques suitable for this purpose are solid state Nuclear Magnetic Resonance (NMR), X-ray powder diffraction (compare FIGS. 1A & B with FIG. 1C), X-ray crystallography, Differential Scanning Calorimetry (DSC), dynamic vapor sorption/desorption (DVS), Karl Fischer analysis (KF), hot stage microscopy, modulated differential screening calorimetry, FT-IR, and Raman spectroscopy. In particular, analysis of the XRPD and DSC data can distinguish Form A, Form B, and a hemibenzenate forms of CDDO-Me. See U.S. Patent Application Publication 2009/0048204, which is incorporated by reference herein in its entirety.

Additional details regarding polymorphic forms of CDDO-Me are described in U.S. Patent Application Publication 2009/0048204, PCT Publication WO 2009/023232 and PCT Publication WO 2010/093944, which are both incorporated herein by reference in their entireties.

Non-limiting specific formulations of the compounds disclosed herein include CDDO-Me polymer dispersions. See, for example, PCT Publication WO 2010/093944,

which is incorporated herein by reference in its entirety.Some of the formulations reported therein exhibited higher bioavailability than either the micronized Form A or nanocrystalline Form A formulations. Additionally, the polymer dispersion based formulations demonstrated further surprising improvements in oral bioavailability relative to the micronized Form B formulations. For example, the methacrylic acid copolymer, Type C and HPMC-P formulations showed the greatest bioavailability in the subject monkeys. See, for example, PCT Publication WO 2010/093944, which is incorporated herein by reference in its entirety.

Compounds employed in methods of the invention may also exist in prodrug form. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals, *e.g.*, solubility, bioavailability, manufacturing, *etc.*, the compounds employed in some methods of the invention may, if desired, be delivered in prodrug form. Thus, the invention contemplates prodrugs of compounds of the present invention as well as methods of delivering prodrugs. Prodrugs of the compounds employed in the invention may be prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Accordingly, prodrugs include, for example, compounds described herein in which a hydroxy, amino, or carboxy group is bonded to any group that, when the prodrug is administered to a subject, cleaves to form a hydroxy, amino, or carboxylic acid, respectively.

It should be recognized that the particular anion or cation forming a part of any salt of this invention is not critical, so long as the salt, as a whole, is pharmacologically acceptable. Additional examples of pharmaceutically acceptable salts and their methods of preparation and use are presented in *Handbook of Pharmaceutical Salts: Properties, and Use* (2002), which is incorporated herein by reference.

Compounds employed in methods of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (*e.g.*, higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art for use in the indications stated herein.

V. Diseases Associated with Inflammation and/or Oxidative Stress

Inflammation is a biological process that provides resistance to infectious or parasitic organisms and the repair of damaged tissue. Inflammation is commonly characterized by localized vasodilation, redness, swelling, and pain, the recruitment of leukocytes to the site of

infection or injury, production of inflammatory cytokines such as TNF-α and IL-1, and production of reactive oxygen or nitrogen species such as hydrogen peroxide, superoxide and peroxynitrite. In later stages of inflammation, tissue remodeling, angiogenesis, and scar formation (fibrosis) may occur as part of the wound healing process. Under normal circumstances, the inflammatory response is regulated and temporary and is resolved in an orchestrated fashion once the infection or injury has been dealt with adequately. However, acute inflammation can become excessive and life-threatening if regulatory mechanisms fail. Alternatively, inflammation can become chronic and cause cumulative tissue damage or systemic complications.

Many serious and intractable human diseases involve dysregulation of inflammatory processes, including diseases such as cancer, atherosclerosis, and diabetes, which were not traditionally viewed as inflammatory conditions. In the case of cancer, the inflammatory processes are associated with tumor formation, progression, metastasis, and resistance to therapy. Atherosclerosis, long viewed as a disorder of lipid metabolism, is now understood to be primarily an inflammatory condition, with activated macrophages playing an important role in the formation and eventual rupture of atherosclerotic plaques. Activation of inflammatory signaling pathways has also been shown to play a role in the development of insulin resistance, as well as in the peripheral tissue damage associated with diabetic hyperglycemia. Excessive production of reactive oxygen species and reactive nitrogen species such as superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite is a hallmark of inflammatory conditions. Evidence of dysregulated peroxynitrite production has been reported in a wide variety of diseases (Szabo *et al.*, 2007; Schulz *et al.*, 2008; Forstermann, 2006; Pall, 2007).

Autoimmune diseases such as rheumatoid arthritis, lupus, psoriasis, and multiple sclerosis involve inappropriate and chronic activation of inflammatory processes in affected tissues, arising from dysfunction of self vs. non-self recognition and response mechanisms in the immune system. In neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, neural damage is correlated with activation of microglia and elevated levels of pro-inflammatory proteins such as inducible nitric oxide synthase (iNOS). Chronic organ failure such as renal failure, heart failure, and chronic obstructive pulmonary disease is closely associated with the presence of chronic oxidative stress and inflammation, leading to the development of fibrosis and eventual loss of organ function.

Many other disorders involve oxidative stress and inflammation in affected tissues, including inflammatory bowel disease; inflammatory skin diseases; mucositis related to radiation therapy and chemotherapy; eye diseases such as uveitis, glaucoma, macular degeneration, and various forms of retinopathy; transplant failure and rejection; ischemia-reperfusion injury; chronic pain; degenerative conditions of the bones and joints including osteoarthritis and osteoporosis; asthma and cystic fibrosis; seizure disorders; and neuropsychiatric conditions including schizophrenia, depression, bipolar disorder, post-traumatic stress disorder, attention deficit disorders, autism-spectrum disorders, and eating disorders such as anorexia nervosa. Dysregulation of inflammatory signaling pathways is believed to be a major factor in the pathology of muscle wasting diseases including muscular dystrophy and various forms of cachexia.

A variety of life-threatening acute disorders also involve dysregulated inflammatory signaling, including acute organ failure involving the pancreas, kidneys, liver, or lungs, myocardial infarction or acute coronary syndrome, stroke, septic shock, trauma, severe burns, and anaphylaxis.

Many complications of infectious diseases also involve dysregulation of inflammatory responses. Although an inflammatory response can kill invading pathogens, an excessive inflammatory response can also be quite destructive and in some cases can be a primary source of damage in infected tissues. Furthermore, an excessive inflammatory response can also lead to systemic complications due to overproduction of inflammatory cytokines such as TNF-α and IL-1. This is believed to be a factor in mortality arising from severe influenza, severe acute respiratory syndrome, and sepsis.

The aberrant or excessive expression of either iNOS or cyclooxygenase-2 (COX-2) has been implicated in the pathogenesis of many disease processes. For example, it is clear that NO is a potent mutagen (Tamir and Tannebaum, 1996), and that nitric oxide can also activate COX-2 (Salvemini *et al.*, 1994). Furthermore, there is a marked increase in iNOS in rat colon tumors induced by the carcinogen, azoxymethane (Takahashi *et al.*, 1997). A series of synthetic triterpenoid analogs of oleanolic acid have been shown to be powerful inhibitors of cellular inflammatory processes, such as the induction by IFN-γ of inducible nitric oxide synthase (iNOS) and of COX-2 in mouse macrophages. See Honda *et al.* (2000a); Honda *et al.* (2000b), and Honda *et al.* (2002), which are all incorporated herein by reference.

In one aspect, compounds disclosed herein are characterized by their ability to inhibit the production of nitric oxide in macrophage-derived RAW 264.7 cells induced by exposure

to γ-interferon. They are further characterized by their ability to induce the expression of antioxidant proteins such as NQO1 and reduce the expression of pro-inflammatory proteins such as COX-2 and inducible nitric oxide synthase (iNOS). These properties are relevant to the treatment of a wide array of diseases involving oxidative stress and dysregulation of inflammatory processes including cancer, mucositis resulting from radiation therapy or chemotherapy, autoimmune diseases, cardiovascular diseases including atherosclerosis, ischemia-reperfusion injury, acute and chronic organ failure including renal failure and heart failure, respiratory diseases, diabetes and complications of diabetes, severe allergies, transplant rejection, graft-versus-host disease, neurodegenerative diseases, diseases of the eye and retina, acute and chronic pain, degenerative bone diseases including osteoarthritis and osteoporosis, inflammatory bowel diseases, dermatitis and other skin diseases, sepsis, burns, seizure disorders, and neuropsychiatric disorders.

Without being bound by theory, the activation of the antioxidant/anti-inflammatory Keap1/Nrf2/ARE pathway is believed to be implicated in both the anti-inflammatory and anti-carcinogenic properties of the compounds disclosed herein.

In another aspect, compounds disclosed herein may be used for treating a subject having a condition caused by elevated levels of oxidative stress in one or more tissues. Oxidative stress results from abnormally high or prolonged levels of reactive oxygen species such as superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite (formed by the reaction of nitric oxide and superoxide). The oxidative stress may be accompanied by either acute or chronic inflammation. The oxidative stress may be caused by mitochondrial dysfunction, by activation of immune cells such as macrophages and neutrophils, by acute exposure to an external agent such as ionizing radiation or a cytotoxic chemotherapy agent (*e.g.*, doxorubicin), by trauma or other acute tissue injury, by ischemia/reperfusion, by poor circulation or anemia, by localized or systemic hypoxia or hyperoxia, by elevated levels of inflammatory cytokines and other inflammation-related proteins, and/or by other abnormal physiological states such as hyperglycemia or hypoglycemia.

In animal models of many such conditions, stimulating expression of inducible heme oxygenase (HO-1), a target gene of the Nrf2 pathway, has been shown to have a significant therapeutic effect including models of myocardial infarction, renal failure, transplant failure and rejection, stroke, cardiovascular disease, and autoimmune disease (*e.g.*, Sacerdoti *et al.*, 2005; Abraham & Kappas, 2005; Bach, 2006; Araujo *et al.*, 2003; Liu *et al.*, 2006; Ishikawa *et al.*, 2001; Kruger *et al.*, 2006; Satoh *et al.*, 2006; Zhou *et al.*, 2005; Morse and Choi, 2005;

Morse and Choi, 2002). This enzyme breaks free heme down into iron, carbon monoxide (CO), and biliverdin (which is subsequently converted to the potent antioxidant molecule, bilirubin).

In another aspect, compounds of this invention may be used in preventing or treating tissue damage or organ failure, acute and chronic, resulting from oxidative stress exacerbated by inflammation. Examples of diseases that fall in this category include: heart failure, liver failure, transplant failure and rejection, renal failure, pancreatitis, fibrotic lung diseases (cystic fibrosis and COPD, among others), diabetes (including complications), atherosclerosis, ischemia-reperfusion injury, glaucoma, stroke, autoimmune disease, autism, macular degeneration, and muscular dystrophy. For example, in the case of autism, studies suggest that increased oxidative stress in the central nervous system may contribute to the development of the disease (Chauhan and Chauhan, 2006).

Evidence also links oxidative stress and inflammation to the development and pathology of many other disorders of the central nervous system, including psychiatric disorders such as psychosis, major depression, and bipolar disorder; seizure disorders such as epilepsy; pain and sensory syndromes such as migraine, neuropathic pain or tinnitus; and behavioral syndromes such as the attention deficit disorders. See, *e.g.*, Dickerson *et al.*, 2007; Hanson *et al.*, 2005; Kendall-Tackett, 2007; Lencz *et al.*, 2007; Dudhgaonkar *et al.*, 2006; Lee *et al.*, 2007; Morris *et al.*, 2002; Ruster *et al.*, 2005; McIver *et al.*, 2005; Sarchielli *et al.*, 2006; Kawakami *et al.*, 2006; Ross *et al.*, 2003, which are all incorporated by reference herein. For example, elevated levels of inflammatory cytokines, including TNF, interferon-γ, and IL-6, are associated with major mental illness (Dickerson *et al.*, 2007). Microglial activation has also been linked to major mental illness. Therefore, downregulating inflammatory cytokines and inhibiting excessive activation of microglia could be beneficial in patients with schizophrenia, major depression, bipolar disorder, autism-spectrum disorders, and other neuropsychiatric disorders.

Accordingly, in pathologies involving oxidative stress alone or oxidative stress exacerbated by inflammation, treatment may comprise administering to a subject a therapeutically effective amount of a compound of this invention, such as those described above or throughout this specification. Treatment may be administered preventively, in advance of a predictable state of oxidative stress (*e.g.*, organ transplantation or the administration of radiation therapy to a cancer patient), or it may be administered therapeutically in settings involving established oxidative stress and inflammation.

The compounds disclosed herein may be generally applied to the treatment of inflammatory conditions, such as sepsis, dermatitis, autoimmune disease and osteoarthritis. In one aspect, the compounds of this invention may be used to treat inflammatory pain and/or neuropathic pain, for example, by inducing Nrf2 and/or inhibiting NF-κB.

Compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (*e.g.*, higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art, whether for use in the above-stated indications or otherwise.

In one aspect, the compounds disclosed herein may be used to function as antioxidant inflammation modulators (AIMs) having potent anti-inflammatory properties that mimic the biological activity of cyclopentenone prostaglandins (cyPGs). In one embodiment, the compounds disclosed herein may be used to control the production of pro-inflammatory cytokines by selectively targeting regulatory cysteine residues (RCRs) on proteins that regulate the transcriptional activity of redox-sensitive transcription factors. Activation of RCRs by cyPGs or AIMs has been shown to initiate a pro-resolution program in which the activity of the antioxidant and cytoprotective transcription factor Nrf2 is potently induced, and the activities of the pro-oxidant and pro-inflammatory transcription factors NF-κB and the STATs are suppressed. This increases the production of antioxidant and reductive molecules (*e.g.*, NQO1, HO-1, SOD1, and/or γ-GCS) and/or decreases oxidative stress and the production of pro-oxidant and pro-inflammatory molecules (*e.g.*, iNOS, COX-2, and/or TNF-α).

In some embodiments, the compounds disclosed herein may be used in the treatment and prevention of diseases such as cancer, inflammation, Alzheimer's disease, Parkinson's disease, multiple sclerosis, autism, amyotrophic lateral sclerosis, autoimmune diseases such as rheumatoid arthritis, lupus, and MS, inflammatory bowel disease, all other diseases whose pathogenesis is believed to involve excessive production of either nitric oxide or prostaglandins, and pathologies involving oxidative stress alone or oxidative stress exacerbated by inflammation.

Another aspect of inflammation is the production of inflammatory prostaglandins such as prostaglandin E. These molecules promote vasodilation, plasma extravasation, localized pain, elevated temperature, and other symptoms of inflammation. The inducible

form of the enzyme COX-2 is associated with their production, and high levels of COX-2 are found in inflamed tissues. Consequently, inhibition of COX-2 may relieve many symptoms of inflammation and a number of important anti-inflammatory drugs (*e.g.*, ibuprofen and celecoxib) act by inhibiting COX-2 activity. Recent research, however, has demonstrated that a class of cyclopentenone prostaglandins (cyPGs) (*e.g.*, 15-deoxy prostaglandin J2, a.k.a. PGJ2) plays a role in stimulating the orchestrated resolution of inflammation (*e.g.*, Rajakariar *et al.*, 2007). COX-2 is also associated with the production of cyclopentenone prostaglandins. Consequently, inhibition of COX-2 may interfere with the full resolution of inflammation, potentially promoting the persistence of activated immune cells in tissues and leading to chronic, "smoldering" inflammation. This effect may be responsible for the increased incidence of cardiovascular disease in patients using selective COX-2 inhibitors for long periods of time.

In one aspect, the compounds disclosed herein may be used to control the production of pro-inflammatory cytokines within the cell by selectively activating regulatory cysteine residues (RCRs) on proteins that regulate the activity of redox-sensitive transcription factors. Activation of RCRs by cyPGs has been shown to initiate a pro-resolution program in which the activity of the antioxidant and cytoprotective transcription factor Nrf2 is potently induced and the activities of the pro-oxidant and pro-inflammatory transcription factors NF-κB and the STATs are suppressed. In some embodiments, this increases the production of antioxidant and reductive molecules (NQO1, HO-1, SOD1, γ-GCS) and decreases oxidative stress and the production of pro-oxidant and pro-inflammatory molecules (iNOS, COX-2, TNF-α). In some embodiments, the compounds of this invention may cause the cells that host the inflammatory event to revert to a non-inflammatory state by promoting the resolution of inflammation and limiting excessive tissue damage to the host.

A. Obesity

Another aspect of the present disclosure concerns new methods and compounds for the treatment and prevention of obesity. Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health. It is typically defined by body mass index (BMI) and may be further evaluated in terms of fat distribution via the waist–hip ratio and total cardiovascular risk factors. BMI is related to both percentage body fat and total body fat.

BMI is calculated by dividing the subject's mass by the square of his or her height (in metric units: kilograms/meters^2). The definitions established by the World Health Organization (WHO) in 1997 and published in 2000 are listed below:

BMI	Classification
< 18.5	underweight
18.5–24.9	normal weight
25.0–29.9	overweight
30.0–34.9	class I obesity
35.0–39.9	class II obesity
≥ 40.0	class III obesity

Obesity increases the risk of many physical and mental conditions. These comorbidities are most commonly shown in metabolic syndrome, a combination of medical disorders which includes: diabetes mellitus type 2, high blood pressure, high blood cholesterol, and high triglyceride levels.

A substantial body of research supports an association between obesity and a chronic, "smoldering" inflammatory state. Obesity is associated with overproduction of inflammatory cytokines and chronic activation of inflammatory signaling pathways, including the NF-kB pathway (Hotamisligil, 2006). Chronic inflammation in adipose tissue is linked with the development of insulin resistance in skeletal muscle (Guilherme *et al.*, 2008). Chronic activation of the NF-κB pathway has been shown to induce insulin resistance and NF-κB inhibition has been proposed as a therapeutic strategy for the treatment of Type 2 diabetes (Arkan *et al.*, 2005; Shoelson *et al.*, 2006).

In a fashion analogous to the development of insulin resistance, obesity has been associated with the development of resistance to the action of leptin. Leptin, a peptide hormone, has complex biological effects but one important site of action is the mediobasal hypothalamus. This structure of the brain is known to exert control over feeding behavior and energy homeostasis. Recently, oxidative stress and activation of the NF-κB pathway in the hypothalamus were shown to be linked to hypothalamic insulin and leptin resistance (Zhang *et al.*, 2008). Activation of the antioxidant transcription factor Nrf2 is known to

inhibit NF-κB activity, and Nrf2 activation by a semisynthetic triterpenoid has been reported to inhibit the development of obesity in mice fed on a high-fat diet (Shin *et al.*, 2009).

The effect of Nrf2 activation on body weight in adult humans with established obesity, however, has not been reported. In the course of a clinical trial of bardoxolone methyl (BARD), in patients with chronic kidney disease and Type 2 diabetes, the inventors noted that essentially all patients treated with bardoxolone methyl lost significant amounts of body weight over a two-month period. The primary purpose of the trial was to study the effects of BARD on parameters related to renal function, with secondary endpoints related to glycemic control and cardiovascular disease. Body weight measurements were a routine component of the safety dataset for this trial. Treatment with BARD produced statistically significant improvements in measures of renal function (serum creatinine, estimated glomerular filtration rate, serum phosphorus, blood urea nitrogen, and uricemia), glycemic control (fasting glucose and hemoglobin A1c percentage), and cardiovascular disease (circulating endothelial cells). The ability of BARD to promote weight loss, while simultaneously improving a variety of measures related to obesity-associated diseases, is both fortuitous and unprecedented.

In a clinical trial of bardoxolone methyl in patients having Type 2 diabetes and chronic kidney disease, designed to measure the drug's effect on measures of kidney function, glycemic control, insulin resistance, and cardiovascular disease, clear improvements in all these parameters were noted. *See* Example 1, below. Patients received 25 mg bardoxolone methyl once per day for 28 days, followed by 75 mg once per day for 28 days. In this study, the protocol stipulated that patient weights were to be taken at baseline (D-1 = 1 day before initiation of dosing), Day 28, and Day 56. Weight data were available for all but one patient who started the study (a baseline weight was not recorded for this patient). In the remaining patients, 14 of 17 had lost weight at Day 28 (mean weight loss was 1.6% of baseline weight) and 17 of 17 had lost weight at Day 56 (mean weight loss was 3.7% of baseline, with a median of 3.1%). All patients, including the patient who did not have a baseline weight available, lost weight between Day 28 and Day 56. A large majority of these patients was overweight or clinically obese (Mean baseline weight was 101 kg). As shown in Table 1, all but three patients lost more than 2% of their baseline weight between Day -1 and Day 56. In general, the drug was very well tolerated in these patients.

This combination of effects (weight loss and improvement in measures related to glycemic control, cardiovascular disease, and renal function) is highly useful. As noted

above, many drugs that have shown the ability to induce weight loss have also shown unacceptable side effects. In addition to its excellent overall tolerability profile, bardoxolone methyl has shown beneficial effects in measures related to several serious obesity-related diseases.

A twelve-month toxicity study for bardoxolone methyl was also conducted on cynomolgus monkeys and their weight was monitored. All the animals were healthy and within normal weights for their age at the start of the study. Interestingly, all groups of animals treated with bardoxolone methyl gained significant amounts of weight at both 26 weeks and 50 weeks. This is consistent with the observation that BARD does not indiscriminately induce weight loss. Instead, in some embodiments its effects appear to be selective to those patients that are overweight and/or obese.

B. Renal Failure

Renal failure, resulting in inadequate clearance of metabolic waste products from the blood and abnormal concentrations of electrolytes in the blood, is a significant medical problem throughout the world, especially in developed countries. *See* U.S. Patent Application Publication 2009/0326063A1, which is incorporated by reference herein in its entirety. Diabetes and hypertension are among the most important causes of chronic renal failure (CKD), but it is also associated with other conditions such as lupus. Acute renal failure may arise from exposure to certain drugs (*e.g.*, acetaminophen) or toxic chemicals, or from ischemia-reperfusion injury associated with shock or surgical procedures such as transplantation, and may result in chronic renal failure. In many patients, renal failure advances to a stage in which the patient requires regular dialysis or kidney transplantation to continue living. Both of these procedures are highly invasive and associated with significant side effects and quality of life issues. Although there are effective treatments for some complications of renal failure, such as hyperparathyroidism and hyperphosphatemia, no available treatment has been shown to halt or reverse the underlying progression of renal failure. Thus, agents that can improve compromised renal function would represent a significant advance in the treatment of renal failure.

Inflammation contributes significantly to the pathology of CKD. There is also a strong mechanistic link between oxidative stress and renal dysfunction. The NF-κB signaling pathway plays an important role in the progression of CKD as NF-κB regulates the transcription of MCP-1, a chemokine that is responsible for the recruitment of monocytes/macrophages resulting in an inflammatory response that ultimately injures the

kidney (Wardle, 2001). The Keap1/Nrf2/ARE pathway controls the transcription of several genes encoding antioxidant enzymes, including heme oxygenase-1 (HO-1). Ablation of the Nrf2 gene in female mice results in the development of lupus-like glomerular nephritis (Yoh *et al.*, 2001). Furthermore, several studies have demonstrated that HO-1 expression is induced in response to renal damage and inflammation and that this enzyme and its products – bilirubin and carbon monoxide – play a protective role in the kidney (Nath *et al.*, 2006).

The glomerulus and the surrounding Bowman's capsule constitute the basic functional unit of the kidney. Glomerular filtration rate (GFR) is the standard measure of renal function. Creatinine clearance is commonly used to measure GFR. However, the level of serum creatinine is commonly used as a surrogate measure of creatinine clearance. For instance, excessive levels of serum creatinine are generally accepted to indicate inadequate renal function and reductions in serum creatinine over time are accepted as an indication of improved renal function. Normal levels of creatinine in the blood are approximately 0.6 to 1.2 milligrams (mg) per deciliter (dl) in adult males and 0.5 to 1.1 milligrams per deciliter in adult females.

Acute kidney injury (AKI) can occur following ischemia-reperfusion, treatment with certain pharmacological agents such as cisplatin and rapamycin, and intravenous injection of radiocontrast media used in medical imaging. As in CKD, inflammation and oxidative stress contribute to the pathology of AKI. The molecular mechanisms underlying radiocontrast-induced nephropathy (RCN) are not well understood; however, it is likely that a combination of events including prolonged vasoconstriction, impaired kidney autoregulation, and direct toxicity of the contrast media all contribute to renal failure (Tumlin *et al.*, 2006). Vasoconstriction results in decreased renal blood flow and causes ischemia-reperfusion and the production of reactive oxygen species. HO-1 is strongly induced under these conditions and has been demonstrated to prevent ischemia-reperfusion injury in several different organs, including the kidney (Nath *et al.*, 2006). Specifically, induction of HO-1 has been shown to be protective in a rat model of RCN (Goodman *et al.*, 2007). Reperfusion also induces an inflammatory response, in part though activation of NF-κB signaling (Nichols, 2004). Targeting NF-κB has been proposed as a therapeutic strategy to prevent organ damage (Zingarelli *et al.*, 2003).

C. Cardiovascular Disease

Cardiovascular (CV) disease is among the most important causes of mortality worldwide, and is the leading cause of death in many developed nations. *See* U.S. Patent

Application Publication 2009/0326063A1, which is incorporated by reference herein in its entirety. The etiology of CV disease is complex, but the majority of causes are related to inadequate or completely disrupted supply of blood to a critical organ or tissue. Frequently such a condition arises from the rupture of one or more atherosclerotic plaques, which leads to the formation of a thrombus that blocks blood flow in a critical vessel. Such thrombosis is the principal cause of heart attacks, in which one or more of the coronary arteries is blocked and blood flow to the heart itself is disrupted. The resulting ischemia is highly damaging to cardiac tissue, both from lack of oxygen during the ischemic event and from excessive formation of free radicals after blood flow is restored (a phenomenon known as ischemia-reperfusion injury). Similar damage occurs in the brain during a thrombotic stroke, when a cerebral artery or other major vessel is blocked by thrombosis. Hemorrhagic strokes, in contrast, involve rupture of a blood vessel and bleeding into the surrounding brain tissue. This creates oxidative stress in the immediate area of the hemorrhage, due to the presence of large amounts of free heme and other reactive species, and ischemia in other parts of the brain due to compromised blood flow. Subarachnoid hemorrhage, which is frequently accompanied by cerebral vasospasm, also causes ischemia/reperfusion injury in the brain.

Alternatively, atherosclerosis may be so extensive in critical blood vessels that stenosis (narrowing of the arteries) develops and blood flow to critical organs (including the heart) is chronically insufficient. Such chronic ischemia can lead to end-organ damage of many kinds, including the cardiac hypertrophy associated with congestive heart failure.

Atherosclerosis, the underlying defect leading to many forms of cardiovascular disease, occurs when a physical defect or injury to the lining (endothelium) of an artery triggers an inflammatory response involving the proliferation of vascular smooth muscle cells and the infiltration of leukocytes into the affected area. Ultimately, a complicated lesion known as an atherosclerotic plaque may form, composed of the above-mentioned cells combined with deposits of cholesterol-bearing lipoproteins and other materials (*e.g.*, Hansson and Anton, 2006).

Pharmaceutical treatments for cardiovascular disease include preventive treatments, such as the use of drugs intended to lower blood pressure or circulating levels of cholesterol and lipoproteins, as well as treatments designed to reduce the adherent tendencies of platelets and other blood cells (thereby reducing the rate of plaque progression and the risk of thrombus formation). More recently, drugs such as streptokinase and tissue plasminogen activator have been introduced and are used to dissolve the thrombus and restore blood flow. Surgical treatments include coronary artery bypass grafting to create an alternative blood

supply, balloon angioplasty to compress plaque tissue and increase the diameter of the arterial lumen, and carotid endarterectomy to remove plaque tissue in the carotid artery. Such treatments, especially balloon angioplasty, may be accompanied by the use of stents, expandable mesh tubes designed to support the artery walls in the affected area and keep the vessel open. Recently, the use of drug-eluting stents has become common in order to prevent post-surgical restenosis (renarrowing of the artery) in the affected area. These devices are wire stents coated with a biocompatible polymer matrix containing a drug that inhibits cell proliferation (*e.g.*, paclitaxel or rapamycin). The polymer allows a slow, localized release of the drug in the affected area with minimal exposure of non-target tissues. Despite the significant benefits offered by such treatments, mortality from cardiovascular disease remains high and significant unmet needs in the treatment of cardiovascular disease remain.

As noted above, induction of HO-1 has been shown to be beneficial in a variety of models of cardiovascular disease, and low levels of HO-1 expression have been clinically correlated with elevated risk of CV disease. Compounds disclosed herein, therefore, may be used in treating or preventing a variety of cardiovascular disorders including but not limited to atherosclerosis, hypertension, myocardial infarction, chronic heart failure, stroke, subarachnoid hemorrhage, and restenosis.

D. Diabetes

Diabetes is a complex disease characterized by the body's failure to regulate circulating levels of glucose. *See* U.S. Patent Application Publication 2009/0326063A1, which is incorporated by reference herein in its entirety. This failure may result from a lack of insulin, a peptide hormone that regulates the both the production and absorption of glucose in various tissues. Deficient insulin compromises the ability of muscle, fat, and other tissues to absorb glucose properly, leading to hyperglycemia (abnormally high levels of glucose in the blood). Most commonly, such insulin deficiency results from inadequate production in the islet cells of the pancreas. In the majority of cases this arises from autoimmune destruction of these cells, a condition known as type 1 or juvenile-onset diabetes, but may also be due to physical trauma or some other cause.

Diabetes may also arise when muscle and fat cells become less responsive to insulin and do not absorb glucose properly, resulting in hyperglycemia. This phenomenon is known as insulin resistance, and the resulting condition is known as Type 2 diabetes. Type 2 diabetes, the most common type, is highly associated with obesity and hypertension. Obesity

is associated with an inflammatory state of adipose tissue that is thought to play a major role in the development of insulin resistance (*e.g.*, Hotamisligil, 2006; Guilherme *et al.*, 2008).

Diabetes is associated with damage to many tissues, largely because hyperglycemia (and hypoglycemia, which can result from excessive or poorly timed doses of insulin) is a significant source of oxidative stress. Chronic kidney failure, retinopathy, peripheral neuropathy, peripheral vasculitis, and the development of dermal ulcers that heal slowly or not at all are among the common complications of diabetes. Because of their ability to protect against oxidative stress, particularly by the induction of HO-1 expression, compounds disclosed herein may be used in treatments for many complications of diabetes. As noted above (Cai *et al.*, 2005), chronic inflammation and oxidative stress in the liver are suspected to be primary contributing factors in the development of Type 2 diabetes. Furthermore, PPARγ agonists such as thiazolidinediones are capable of reducing insulin resistance and are known to be effective treatments for Type 2 diabetes.

Based on experimental results obtained, including those presented in this application, the compounds and methods of this invention may be used for treating patients with neuroinflammation.

The effect of treatment of diabetes may be evaluated as follows. Both the biological efficacy of the treatment modality as well as the clinical efficacy are evaluated, if possible. For example, disease manifests itself by increased blood sugar, the biological efficacy of the treatment therefore can be evaluated, for example, by observation of return of the evaluated blood glucose towards normal. Measuring a clinical endpoint which can give an indication of b-cell regeneration after, for example, a six-month period of time, can give an indication of the clinical efficacy of the treatment regimen.

E. Liver Disease

Liver disease (also called hepatic disease) is a broad term describing any single number of diseases affecting the liver. Many are accompanied by jaundice caused by increased levels of bilirubin in the system. The bilirubin results from the breakup of the hemoglobin of dead red blood cells; normally, the liver removes bilirubin from the blood and excretes it through bile.

Various types of liver disease include:

Hepatitis, inflammation of the liver, caused mainly by various viruses but also by some poisons (*e.g.*, alcohol), autoimmunity (autoimmune hepatitis) or hereditary conditions;

Non-alcoholic fatty liver disease, a spectrum in disease, associated with obesity and characterized as an abundance of fat in the liver; may lead to a hepatitis, *i.e.*, steatohepatitis and/or cirrhosis;

Cirrhosis (the formation of fibrous tissue in the liver, replacing dead liver cells), cause by viral hepatitis, alcoholism or contact with other liver-toxic chemicals;

Haemochromatosis, a hereditary disease causing the accumulation of iron in the body, eventually leading to liver damage;

Cancer of the liver (primary hepatocellular carcinoma or cholangiocarcinoma and metastatic cancers, usually from other parts of the gastrointestinal tract);

Wilson's disease, a hereditary disease which causes the body to retain copper;

Primary sclerosing cholangitis, an inflammatory disease of the bile duct, likely autoimmune in nature;

Primary biliary cirrhosis, autoimmune disease of small bile ducts;

Budd-Chiari syndrome, obstruction of the hepatic vein;

Gilbert's syndrome, a genetic disorder of bilirubin metabolism, found in about 5% of the population; and

Glycogen storage disease type II, the build-up of glycogen causes progressive muscle weakness (myopathy) throughout the body and affects various body tissues, particularly in the heart, skeletal muscles, liver and nervous system.

There are also many pediatric liver disease, including biliary atresia, alpha-1 antitrypsin deficiency, alagille syndrome, and progressive familial intrahepatic cholestasis, to name but a few.

The external signs of liver disease include a coated tongue, bad breath, itchy skin, excessive sweating, offensive body odor, dark circles under the eyes, red swollen and itchy eyes, acne rosacea, brownish spots and blemishes on the skin, flushed facial appearance or excessive facial blood vessels. Other symptoms include jaundice, dark urine, pale stool, bone loss, easy bleeding, itching, small, spider-like blood vessels visible in the skin, enlarged spleen, fluid in the abdominal cavity, chills, pain from the biliary tract or pancreas, and an enlarged gallbladder.

The symptoms related to liver dysfunction include both physical signs and a variety of symptoms related to digestive problems, blood sugar problems, immune disorders, abnormal absorption of fats, and metabolism problems. The malabsorption of fats may lead to symptoms that include indigestion, reflux, deficit of fatsoluble vitamins, hemorrhoids, gall

stones, intolerance to fatty foods, intolerance to alcohol, nausea and vomiting attacks, abdominal bloating, and constipation.

Nervous system disorders include depression, mood changes, especially anger and irritability, poor concentration and "foggy brain," overheating of the body, especially the face and torso, and recurrent headaches (including migraine) associated with nausea. The blood sugar problems include a craving for sugar, hypoglycaemia and unstable blood sugar levels, and the onset of type 2 diabetes.

Abnormalities in the level of fats in the blood stream include high or low levels of lipids. Hypercholesterolemia includes elevated LDL cholesterol, reduced HDL cholesterol, elevated triglycerides, clogged arteries leading to high blood pressure heart attacks and strokes, build up of fat in other body organs (fatty degeneration of organs), lumps of fat in the skin (lipomas and other fatty tumors), excessive weight gain (which may lead to obesity), inability to lose weight even while dieting, sluggish metabolism, protuberant abdomen (pot belly), cellulite, and/or fatty liver. Hypocholesterolemia is low total cholesterol, low LDL and VLDL cholesterol, and/or low triglyderides.

A number of liver function tests are available to test the proper function of the liver. These test for the presence of enzymes in blood that are normally most abundant in liver tissue, metabolites or products. If alcohol-induced liver disease is suspected, blood tests and imaging tests (MRI, CT scan, or ultrasound) may help in diagnosis and to rule out other causes of liver disease but proof is best established by liver biopsy.

A specific X-ray known as the hepatic angiography is used to investigate the veins and arteries that supply blood to the liver. Usually an X-ray is requested only if the CT scan or MRI do not show conclusive information. During a hepatic angiography, a thin and flexible tube is inserted into a blood vessel through a cut into the groin. Then a dye is injected, which lights up the blood vessels for better visualization. This procedure is generally performed under local anesthetic and it is not painful but may be uncomfortable.

Medical imaging tests allow doctors to examine a patient by looking at still and moving images of their internal organs and tissue One of the first tests a patient may be required to take is the ultrasound. This is a routine procedure that is not harmful in any way to the patient since it does not utilize radioactive waves. It normally takes up to 15 minutes to be completed. Before the procedure is performed, a gel is applied on the skin. Its main purposes are to promote easy movements and to make sure that wave sounds are directed through the skin. The solid masses are turned into images that are seen on a monitor by a

radiologist. The pictures are recorded and the radiologist will make a report which is to be discussed with the patient's doctor during a specific appointment.

CT scans or computed tomography is a painless procedure used in order to obtain pictures of the body organs and tissues. Unlike the ultrasound, the CT scan uses radiation but with minimal risks. The tomograms taken by a CT scanner can show if there are any abnormalities in the lungs, bones, soft tissues and blood vessels. It is mostly used for studying the abdomen and chest and it can take up to 30 minutes. The CT scanner is a large machine, in which the patient is moved forward and backwards. Before the test is taken, the patient gets an iodine dye into a vein which helps visualizing blood vessels and kidneys and also makes it easier to observe differences between normal and abnormal tissue in the liver and other organs.

Magnetic resonance imaging (MRI) is able to get more detailed images than a CT scan. It is a new technology, a kind of a tube scanner used to create magnetic fields by releasing radio frequency energy. The MRI is mostly used to observe and investigate tumors before and after treatment. It is not a painful procedure and a regular scan session does not usually takes more than 30 minutes. However, some patients may feel claustrophobic during the scan. Some of the patients who have specific implants may not have a MRI due to the existence of metal in their bodies.

The treatment of liver disease is different depending on the type of condition. Liver diseases affect the proper functioning of the liver. Treoatment for liver diseases is normally directed towards the relief of symptoms and complications. Most of the time is focused on avoiding the risk factors.

All types of hepatitis are addressed with intravenous therapy fluids due to the dehydration caused by vomiting and diarrhea. Usually, patients whose symptoms are not severe, can treat the disease at home, otherwise, hospitalization may be needed. Medication for nausea and vomiting is also available. Hepatitis B and C may become chronic and unfortunately, there is no medication that can prevent this to happen. Once hepatitis B becomes chronic, it may be treated with antiviral drugs but this type of medication is not effective on all patients. Chronic hepatitis C is treated with the so called pegylated interferon alpha agent (Pegasys or PEG-Intron) that may be combined with an antiviral called ribavirin. The treatment for chronic hepatitis B and C is given based on the results of several tests regarding the functioning of the liver and the type of medication administrated is decided after consulting a gastroenterologist and a liver specialist. However, the usage of interferon in

order to treat hepatitis C may be restricted in cases of active alcohol abuse or drug abuse, in cases of depression, autoimmune diseases or low hemoglobin levels.

Treatment for cirrhosis is mainly directed towards the relief of complications. Medication may be used to treat the underlying cause. Some of these include steroids, penicillamine and an anti-inflammatory agent such as colchicine. Their effect is still being studied and at this moment they do not seem to improve the patient's condition. Cirrhosis caused by portal hypertension may be treated with β blockers that lower the blood pressure.

VI. Pharmaceutical Formulations and Routes of Administration

The compounds of the present disclosure may be administered by a variety of methods, *e.g.*, orally or by injection (*e.g.* subcutaneous, intravenous, intraperitoneal, *etc.*). Depending on the route of administration, the active compounds may be coated in a material to protect the compound from the action of acids and other natural conditions which may inactivate the compound. They may also be administered by continuous perfusion/infusion of a disease or wound site.

The compounds of the present disclosure may also be formulated and/or prepared in a variety of ways, including as a solid dispersion. See, for example, PCT Publication WO 2010/093944, which is incorporated herein by reference in its entirety.

To administer the therapeutic compound by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the therapeutic compound may be administered to a patient in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan *et al.*, 1984).

The therapeutic compound may also be administered parenterally, intraperitoneally, intraspinally, or intracerebrally. Liquid or semi-liquid dispersions can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases, the composition must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating

action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (such as, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

Sterile injectable solutions can be prepared by incorporating the therapeutic compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the therapeutic compound into a sterile carrier which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient (*i.e.*, the therapeutic compound) plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The therapeutic compound can be orally administered, for example, with an inert diluent or an assimilable edible carrier. The therapeutic compound and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. In some embodiments, the compound, for example bardoxolone methyl, is formulated as a capsule. For oral therapeutic administration, the therapeutic compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. In some embodiments, the compound, for example bardoxolone methyl, is formulated as an ingestible tablet. The percentage of the therapeutic compound in the compositions and preparations may, of course, be varied. The amount of the therapeutic compound in such therapeutically useful compositions is such that a suitable dosage will be obtained.

In some embodiments the daily dose of the therapeutic compound for human patients will be from 5 mg to 500 mg. In some of these embodiments, the dose will be from 10 mg to 300 mg. In some of these embodiments, the dose will be from 10 mg to 250 mg. In some of these embodiments, the dose will be from 25 mg to 150 mg. For example in some embodiments, the daily dose of bardoxolone methyl will be about 25 mg, about 75 mg or about 150 mg. In some embodiments, about 25 mg, about 75 mg or about 150 mg of bardoxolone methyl may be incorporated with expedients and/or other pharmaceutically suitable ingredients into an ingestible capsule or tablet. In some of these embodiments, the form of the bardoxolone methyl will be Form A.

In some embodiments the daily dose of the therapeutic compound for human patients will be from 5 mg to 50 mg. In some of these embodiments, the dose will be from 10 mg to 40 mg. For example in some embodiments, the daily dose of bardoxolone methyl will be about 10 mg, about 20 mg or about 40 mg. In some embodiments, about 10 mg, about 20 mg or about 40 mg of bardoxolone methyl may be incorporated with expedients and/or other pharmaceutically suitable ingredients into an ingestible capsule or tablet. In some of these embodiments, the form of the bardoxolone methyl will be Form B. In some of these embodiments, the form of the bardoxolone methyl will be a solid dispersion of Form B. See, for example, PCT Publication WO 2010/093944, which is incorporated herein by reference in its entirety.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit containing a predetermined quantity of therapeutic compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the therapeutic compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such a therapeutic compound for the treatment of a selected condition in a patient.

Active compounds are administered at a therapeutically effective dosage sufficient to treat a condition associated with a condition in a patient. For example, the efficacy of a compound can be evaluated in an animal model system that may be predictive of efficacy in treating the disease in humans, such as the model systems shown in the examples and drawings.

The actual dosage amount of a compound of the present disclosure or composition comprising a compound of the present disclosure administered to a subject may be determined by physical and physiological factors such as age, sex, body weight, severity of condition, the type of disease being treated, previous or concurrent therapeutic interventions, idiopathy of the subject and on the route of administration. These factors may be determined by a skilled artisan. The practitioner responsible for administration will typically determine the concentration of active ingredient(s) in a composition and appropriate dose(s) for the individual subject. The dosage may be adjusted by the individual physician in the event of any complication.

In addition to the dosages disclosed above, the an effective amount of the compounds may vary from about 0.001 mg/kg to about 1000 mg/kg, from about 0.01 mg/kg to about 750 mg/kg, from about 100 mg/kg to about 500 mg/kg, from about 1.0 mg/kg to about 250 mg/kg, from about 10.0 mg/kg to about 150 mg/kg in one or more dose administrations daily, for one or several days (depending of course of the mode of administration and the factors discussed above). Other suitable dose ranges include 1 mg to 10000 mg per day, 100 mg to 10000 mg per day, 500 mg to 10000 mg per day, and 500 mg to 1000 mg per day. In some particular embodiments, the amount is less than 10,000 mg per day with a range of 750 mg to 9000 mg per day.

The effective amount may be less than 500 mg/kg/day, less than 250 mg/kg/day, less than 100 mg/kg/day, less than 50 mg/kg/day, less than 25 mg/kg/day, less than 10 mg/kg/day or less than less than 1 mg/kg/day. It may alternatively be in the range of 1 mg/kg/day to 200 mg/kg/day. For example, regarding treatment of diabetic patients, the unit dosage may be an amount that reduces blood glucose by at least 40% as compared to an untreated subject. In another embodiment, the unit dosage is an amount that reduces blood glucose to a level that is ± 10% of the blood glucose level of a non-diabetic subject.

In other non-limiting examples, a dose may also comprise from about 1 microgram/kg/body weight, about 5 microgram/kg/body weight, about 10 microgram/kg/body weight, about 50 microgram/kg/body weight, about 100 microgram/kg/body weight, about 200 microgram/kg/body weight, about 350 microgram/kg/body weight, about 500 microgram/kg/body weight, about 1 milligram/kg/body weight, about 5 milligram/kg/body weight, about 10 milligram/kg/body weight, about 50 milligram/kg/body weight, about 100 milligram/kg/body weight, about 200 milligram/kg/body weight, about 350 milligram/kg/body weight, about 500 milligram/kg/body weight, to about 1000 mg/kg/body weight or more per administration, and any range derivable therein. In non-limiting examples

of a derivable range from the numbers listed herein, a range of about 5 mg/kg/body weight to about 100 mg/kg/body weight, about 5 microgram/kg/body weight to about 500 milligram/kg/body weight, *etc.*, can be administered, based on the numbers described above.

In certain embodiments, a pharmaceutical composition of the present disclosure may comprise, for example, at least about 0.1% of a compound of the present disclosure. In other embodiments, the compound of the present disclosure may comprise between about 2% to about 75% of the weight of the unit, or between about 25% to about 60%, for example, and any range derivable therein.

Single or multiple doses of the agents are contemplated. Desired time intervals for delivery of multiple doses can be determined by one of ordinary skill in the art employing no more than routine experimentation. As an example, subjects may be administered two doses daily at approximately 12 hour intervals. In some embodiments, the agent is administered once a day.

The agent(s) may be administered on a routine schedule. As used herein a routine schedule refers to a predetermined designated period of time. The routine schedule may encompass periods of time which are identical or which differ in length, as long as the schedule is predetermined. For instance, the routine schedule may involve administration twice a day, every day, every two days, every three days, every four days, every five days, every six days, a weekly basis, a monthly basis or any set number of days or weeks there-between. Alternatively, the predetermined routine schedule may involve administration on a twice daily basis for the first week, followed by a daily basis for several months, *etc.* In other embodiments, the invention provides that the agent(s) may taken orally and that the timing of which is or is not dependent upon food intake. Thus, for example, the agent can be taken every morning and/or every evening, regardless of when the subject has eaten or will eat.

VII. Combination Therapy

In addition to being used as a monotherapy, the compounds of the present invention may also find use in combination therapies. Effective combination therapy may be achieved with a single composition or pharmacological formulation that includes both agents, or with two distinct compositions or formulations, administered at the same time, wherein one composition includes a compound of this invention, and the other includes the second agent(s). Alternatively, the therapy may precede or follow the other agent treatment by intervals ranging from minutes to months.

Various combinations may be employed, such as when a compound of the present invention is "A" and "B" represents a secondary agent, non-limiting examples of which are described below:

A/B/A	B/A/B	B/B/A	A/A/B	A/B/B	B/A/A	A/B/B/B	B/A/B/B
B/B/B/A	B/B/A/B	A/A/B/B	A/B/A/B	A/B/B/A	B/B/A/A		
B/A/B/A	B/A/A/B	A/A/A/B	B/A/A/A	A/B/A/A	A/A/B/A		

It is contemplated that other anti-inflammatory agents may be used in conjunction with the treatments of the current invention. For example, other COX inhibitors may be used, including arylcarboxylic acids (salicylic acid, acetylsalicylic acid, diflunisal, choline magnesium trisalicylate, salicylate, benorylate, flufenamic acid, mefenamic acid, meclofenamic acid and triflumic acid), arylalkanoic acids (diclofenac, fenclofenac, alclofenac, fentiazac, ibuprofen, flurbiprofen, ketoprofen, naproxen, fenoprofen, fenbufen, suprofen, indoprofen, tiaprofenic acid, benoxaprofen, pirprofen, tolmetin, zomepirac, clopinac, indomethacin and sulindac) and enolic acids (phenylbutazone, oxyphenbutazone, azapropazone, feprazone, piroxicam, and isoxicam. See also U.S. Patent 6,025,395, which is incorporated herein by reference.

Dietary and nutritional supplements with reported benefits for treatment or prevention of Parkinson's, Alzheimer's, multiple sclerosis, amyotrophic lateral sclerosis, rheumatoid arthritis, inflammatory bowel disease, and all other diseases whose pathogenesis is believed to involve excessive production of either nitric oxide (NO) or prostaglandins, such as acetyl-L-carnitine, octacosanol, evening primrose oil, vitamin B6, tyrosine, phenylalanine, vitamin C, L-dopa, or a combination of several antioxidants may be used in conjunction with the compounds of the current invention.

Other particular secondary therapies include immunosuppressants (for transplants and autoimmune-related RKD), anti-hypertensive drugs (for high blood pressure-related RKD, *e.g.*, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), insulin (for diabetic RKD), lipid/cholesterol-lowering agents (*e.g.*, HMG-CoA reductase inhibitors such as atorvastatin or simvastatin), treatments for hyperphosphatemia or hyperparathyroidism associated with CKD (*e.g.*, sevelamer acetate, cinacalcet), dialysis, and dietary restrictions (*e.g.*, protein, salt, fluid, postassium, phosphorus).

VIII. Examples

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1 – Clinical Weight Reduction Data in Phase 2 Study

In a clinical trial of bardoxolone methyl in patients having Type 2 diabetes and chronic kidney disease, designed to measure the drug's effect on measures of kidney function, glycemic control, insulin resistance, and cardiovascular disease, clear improvements in all these parameters were noted. *See* U.S. Patent Application Publication 2009/0326063A1, which is incorporated by reference herein in its entirety.

Patients received 25 mg bardoxolone methyl once per day for 28 days (given orally in capsule form), followed by 75 mg once per day for 28 days (given orally in capsule form). In this study, the protocol stipulated that patient weights were to be taken at baseline (D-1 = 1 day before initiation of dosing), Day 28, and Day 56. Weight data were available for all but one patient who started the study (a baseline weight was not recorded for this patient). In the remaining patients, 14 of 17 had lost weight at Day 28 (mean weight loss was 1.6% of baseline weight) and 17 of 17 had lost weight at Day 56 (mean weight loss was 3.7% of baseline, with a median of 3.1%). All patients, including the patient who did not have a baseline weight available, lost weight between Day 28 and Day 56. A large majority of these patients were overweight or clinically obese (Mean baseline weight was 101 kg). As shown in Table 1, all but three patients lost more than 2% of their baseline weight between Day -1 and Day 56. In general, the drug was very well tolerated in these patients. Additional patient data is provided in Tables 2 and 3.

Prior to initiation of treatment, basic clinical observations (*e.g.*, weight, blood pressure, height) were recorded along with baseline values for serum creatinine, blood urea nitrogen, serum phosphorus, serum uric acid, angiotensin II, fasting glucose, hemoglobin A1c, circulating endothelial cells (CECs), and iNOS-positive CECs.

Parameters related to renal function improved significantly after 28 days of treatment (eGFR increased approximately 10%) and still further after 56 days of treatment (eGFR increased more than 20% compared to baseline). Reductions of more than 10% were also observed in BUN, serum creatinine, uric acid, and urinary albumin/creatinine ratio. Significant reductions in CECs and iNOS-positive CECs were also noted. Results are summarized in Table 4.

Table 1. Weigh Levels and Percent Change in Response to Bardoxolone Methyl in Chronic Kidney Disease (CKD) Patients

Patient ID	Start Dose	Escalated Dose	Weight (kg)				
	(mg)	(mg)	D-1	D28	D56	Percent Change D28/D-1	Percent Change D56/D-1
032	25	75	88.0	88.0	87.1	0.0%	-1.0%
033	25	75	80.7	80.7	75.7	0.0%	-6.2%
036	25	75	76.2	75.7	74.4	-0.7%	-2.4%
029	25	75	111.6	108.9	107.0	-2.4%	-4.1%
045	25	75	81.6	80.3	78.5	-1.6%	-3.8%
039	25	75	104.3	100.7	97.1	-3.5%	-6.9%
044	25	75	111.6	108.9	108.0	-2.4%	-3.2%
047	25	75	114.3	112.9	111.1	-1.2%	-2.8%
038	25	75	86.2	78.9	77.1	-8.5%	-10.6%
049	25	75	89.8	88.5	88	-1.4%	-2.0%
050	25	75	N/A	104.3	102.1	N/A	N/A
084	25	75	169.4	169.3	165.9	-0.1%	-2.1%
051	25	75	60.3	52.6	52.2	-12.8%	-13.4%
052	25	75	83.9	83.5	80.3	-0.5%	-4.3%
055	25	75	159.2	159.7	157.9	0.3%	-0.8%
102	25	75	114.4	114	110.4	-0.3%	-3.5%
008	25	N/A	93.0	92.1	91.6	-1.0%	-1.5%
100	25	N/A	92.7	89.9	87.4	-3.0%	-5.7%
Mean		**All**	101.0	99.4	97.3	-1.6%	-3.7%

Table 2. Additional Patient Data

Patient ID	Age	Sex	Diabetes Duration	ACE	ARB	Other Renal	Statin	Insulin	Epo and Related Drugs	Non-renal Diabetic Complications	Hypertensive
032	87	M	49	N	Y	Y	Y	N	Y	Y	Y
033	76	F	8	N	Y	Y	N	N	N	N	Y
036	63	F	15	N	Y	Y	Y	Y	N	N	Y
029	50	M	3	N	N	N	Y	N	N	Y	Y
045	62	F	7	N	N	Y	Y	Y	Y	N	Y
039	73	F	26	N	Y	Y	Y	Y	Y	N	Y
044	70	M	1	N	Y	N	Y	N	N	N	Y
047	61	F	15	Y	Y	Y	Y	Y	N	N	Y
038	34	F	10	N	Y	Y	Y	Y	N	N	Y
049	79	F	10	N	N	Y	N	Y	N	Y	Y
050	65	F	5	Y	N	N	Y	Y	N	N	Y
084	61	F	18	Y	N	Y	Y	Y	N	Y	Y
051	71	M	35	N	N	Y	N	N	Y	Y	Y
052	57	F	8	N	Y	Y	Y	Y	N	N	Y
055	60	M	10	Y	N	Y	Y	Y	N	N	Y
102	68	M	29	N	N	Y	Y	Y	N	N	Y
008	56	M	3	N	N	Y	Y	Y	N	Y	Y
100	69	M	26	N	Y	Y	Y	N	N	Y	N

Table 3. Demographics of Patients Completing the Study	**(n=18)**
Average Age (mean)	65
Average Diabetes Duration (in yrs) (mean)	16
Chronic Kidney Disease	100%
Average Baseline eGFR (ml/min/1.73m^2) (mean)	31.0
Stage 4 CKD	50%
Non-Renal Diabetic Complications[1]	50%
Hypertensive	94%
Hgb A1c(%)	7.9%
Failed Oral Antihyperglycemics	67%
On Stable Renal Meds	94%
RAS Blocker	78%
Ca Channel Blocker	39%
Statin Use	83%
[1]Includes neuropathy and retinopathy	

Table 4. Non-Weight Related Results

Summary of Stratum 2 Data	All Patients (n=18)
Patients with eGFR Increase	89%
eGFR	+24.1%***
Serum Creatinine	-17.5%**
Creatinine Clearance	+38.2%†
Urine Albumin to Creatinine Ratio	-14.1%
Blood Urea Nitrogen	-14.9%
Phosphorus	-2.5%
Uric Acid	-13.3%†
Hemoglobin A1c (%; BL ≥7.0%)	-0.1
Circulating Endothelial Cells	-34.8%†
iNOS+ Circulating Endothelial Cells	-65.8%*
†p<0.05; *p<0.01; **p<0.001; ***p<0.0001	

Example 2 – Toxicity Study in Monkeys

Bardoxolone methyl and vehicle were administered once per day for 353 days during the study via oral gavage to a group of cynomolgus monkeys. All the animals were healthy and within normal weights for their age at the start of the study. The dose levels were 0, 30/5, 100/30, and 300 mg/kg/day and administered at a dose volume of 3 mL per dose. The control group received the vehicle in the same manner as the treated groups. Just prior to administration, the test article for each animal was added to the syringe containing the vehicle for each animal and vortexed until thoroughly mixed to achieved the desired concentrations of 30, 100, and 300 mg/mL through Day 42 (Week 6). During administration, the syringe containing the test article preparation for each animal was pushed through the gavage tube. The 1 mL vehicle rinse was then added to the dosing syringe and administered. After administration of both volumes, a 5 mL flush of the vehicle was used to rinse the gavage tube and ensure that the entire amount of the test article was administered to the animal. Analysis of whole blood samples from Days 1 and 28 indicated no significant differences in exposure across the three dose levels. Therefore, dose levels were adjusted so that different blood exposures could be examined. During Week 7 dosing for all animals was stopped for four days (Days 43 to 46). The initial dose levels of 30 and 100 mg/kg/day were reduced to 5 and 30 mg/kg/day, respectively, and dosing was resumed on Day 47 through Day 353. Individual doses were based on the most recent body weights. Results of this study are summarized in Table 5. All treated groups gained weight during the study, indicating that bardoxolone methyl treatment did not induce weight loss in healthy monkeys with normal body weights.

Table 5. Body Weight Observations in 12-Month Toxicology Study of Bardoxolone Methyl in Cynomolgus Monkeys

	Males					Females				
	Pretest Weight (kg)	Week 26 Weight (kg)	Week 50 Weight (kg)	kg gained	% gain	Pretest Weight (kg)	Week 26 Weight (kg)	Week 50 Weight (kg)	kg gained	% gain
Control	2.119	2.791	3.35	1.231	58.09%	2.047	2.608	2.892	0.845	41.28%
30/5	2.128	2.567	2.975	0.847	39.80%	2.069	2.454	2.608	0.539	26.05%
100/30	2.152	2.464	2.725	0.573	26.63%	2.058	2.293	2.68	0.622	30.22%
300	2.141	2.52	2.808	0.667	31.15%	2.084	2.552	2.68	0.596	28.60%

Example 3 – Clinical Weight Reduction Data in Phase 2b/3 Study

The efficacy and safety of bardoxolone methyl were studied in a Phase 2b/3 trial in patients with Stage 3b or Stage 4 CKD and Type 2 diabetes. Weight measurements were included in the study as a basic clinical parameter.

F. Patient Population

The study randomized adults with moderate to severe CKD and type 2 diabetes mellitus who had screening estimated GFR (using the MDRD formula) between 20 and 45 mL/min/1.73 m^2. Screening estimated GFR was calculated as the mean of two estimated GFR results (differing no more than 25%) collected at least 5 days apart within a 3-week period. Treatment with an angiotensin converting enzyme inhibitor, an angiotensin receptor blocker, or both for at least three months with a stable dose for at least eight weeks prior to screening was required; 98% of patients met this criterion. Exclusion criteria included type 1 diabetes, non-diabetic kidney disease, hemoglobin A1c >10%, QTc Fredericia interval > 450 milliseconds, evidence of hepatic dysfunction, and recent cardiovascular disease.

G. Study Design

The study randomized 227 patients 1:1:1:1 to receive placebo, 25, 75, or 150 mg bardoxolone methyl for 52 weeks, inclusive of titration to the assigned dose level. The study had four periods: (1) 21-days of screening/placebo run-in; (2) 8-week titration period to reach the randomized dose, with an extension up to 20 weeks in patients who had trouble tolerating the drug or an abnormal laboratory test result that precluded final titration within 8 weeks; (3) dose maintenance period from end of titration through Week 52; and (4) 4-week follow-up period after the last dose of study drug. Study drug was taken orally once daily in the morning one hour prior to food intake. Dose titration occurred as follows: (1) placebo; (2) 25 mg; (3) 25 mg, increased to 75 mg after 4 weeks; and (4) 25 mg, increased to 75 mg after 4 weeks, further increased to 150 mg after an additional 4 weeks. Randomization was stratified by CKD stage (3b versus 4), urinary albumin to creatinine ratio (ACR; $\leq$ versus > 300 mg/g), and glucose control (hemoglobin A1c < versus $\geq$ 7%). An independent Data Safety Monitoring Board monitored patient safety.

H. Procedures and Outcomes

Estimated GFR and routine safety laboratory testing was done at screening and every four weeks thereafter using a central laboratory. Adverse events and clinical laboratory

parameters were assessed at each visit. Analysis of the primary outcome, change from baseline estimated GFR at Week 24, occurred after all randomized patients completed Week 24 or previously discontinued study. Exploratory outcomes included change from baseline at Week 24 in serum creatinine, blood urea nitrogen, serum phosphorus, uric acid, ACR, hemoglobin A1c, and intact parathyroid hormone.

I. Patient Characteristics

Treatment groups were generally well balanced with respect to baseline variables (Table 6) although the placebo group had a slightly lower percentage of males (49%) than the active groups (59%). Mean age was 67 years. Mean time between diagnosis of diabetes mellitus and randomization was 18 years; diabetes was well controlled with mean baseline hemoglobin A1c of 7.2%. At study entry, mean estimated GFR was 32.4 mL/min/1.73 m^2, with 62% of patients having Stage 3b CKD and 38% having Stage 4 CKD. Median baseline ACR was 596 mg/g. ACR >300 mg/g (macroalbuminuria), 30-300 mg/g (microalbuminuria), and <30 mg/g were each represented by one-third of the patients. Ninety-eight percent of patients were receiving ACE inhibitor, ARB therapy, or both; the remaining patients received a waiver from the inclusion criteria because they were intolerant to these medications.

J. Primary Outcome

At Week 24, all bardoxolone methyl groups showed increases in estimated GFR both relative to baseline and to changes in the placebo group, with mean increases compared to placebo of 8.3 ± 1.1, 11.5 ± 1.1, and 10.6 ± 1.1 mL/min/1.73 m^2 among the 25, 75, and 150 mg groups, respectively ($p<0.001$, all groups). The placebo group showed essentially no change (0.1 ± 1.1 mL/min/1.73 m^2) (Table 7). The difference between the 25 and 75 mg groups was statistically significant (nominal $p=0.039$) but the difference between the 75 and 150 mg groups was not ($p=0.54$). Increases in estimated GFR were observed within 4 weeks of treatment initiation for the bardoxolone methyl groups, peaked at Week 12, and remained stable through Week 24 (FIG. 2). At Week 24, 74% of bardoxolone methyl patients experienced more than a 10% increase in estimated GFR, and 24% of bardoxolone methyl patients reported more than a 50% increase in estimated GFR compared to a single placebo patient (data not shown).

Most patients treated with bardoxolone methyl experienced an improvement in CKD stage from Stage 4 to Stage 3b or from Stage 3b to Stage 3a. The percentages improving were 17% in the placebo group, 53% in the 25 mg group, 69% in the 75 mg group, and 61% in the

150 mg group. Furthermore, fewer patients in each bardoxolone methyl group experienced a worsening of CKD stage than in the placebo group (2 patients [4%] in each bardoxolone methyl group compared to 7 patients [13%] in the placebo group).

Weight was reduced over time in the active treatment cohorts. Mean weight change at Week 24 was −5.9, −4.7, and −5.8 kg in the 25, 75, and 150 mg groups, respectively, while no weight change was observed in the placebo group.

Example 4 – Clinical Weight Reduction Resulting from 12 Months of Treatment

In a continuation of the study described in Example 3, patients remained in their assigned treatment group (placebo, 25 mg bardoxolone methyl/day, 75 mg bardoxolone methyl/day, 150 mg bardoxolone methyl/day) for an additional 28 weeks, bringing the total treatment period to 52 weeks. The double-blinded structure of the study was maintained throughout the 52-week period. At week 52, patients in all treatment groups had lost additional weight relative to week 24. As shown in Table 8, at least two thirds of patients treated with bardoxolone methyl had lost more than 5 kg by week 52, compared to 21% of placebo-treated patients. Approximately one third of patients treated with bardoxolone methyl had lost more than 10 kg by week 52, compared to 6% of placebo-treated patients. Table 9 shows weight data in 4 week increments for each group over the entire 52 week period of treatment. Treatment was discontinued in all groups at week 52 (including the placebo group), and final clinical and laboratory measurements were taken at week 56. The data in Table 9 demonstrate that patients in the bardoxolone methyl treatment groups lost weight at a relatively uniform rate throughout the 52-week treatment period.

Table 6. Demographics and Baseline Characteristics

		Bardoxolone methyl			
	Placebo N=57	*25 mg N=57*	*75 mg N=57*	*150 mg N=56*	*Total N=227*
Demographic Characteristics					
Male, n (%)	28 (49)	34 (60)	33 (58)	33 (59)	128 (56)
Age, mean (SD)	67.7 (10)	66.9 (9.2)	66.1 (8.7)	66.7 (9.2)	66.8 (9.3)
Race, n (%)					
White	44 (77)	44 (77)	41 (72)	44 (79)	173 (76)
Black	10 (18)	10 (18)	11 (19)	11 (20)	42 (19)
Other	3 (5)	3 (5)	5 (9)	1 (2)	12 (5)
Hispanic or Latino, n (%)	18 (32)	12 (21)	21 (37)	11 (20)	62 (27)
Baseline Characteristics	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*
Time from diabetes diagnosis to randomization (years)	17.1 (9.9)	18.2 (10.8)	17.8 (9.8)	18.6 (9.8)	18.0 (10.0)
Weight (kg)	95.2 (22.8)	103.0 (22.9)	97.7 (23.1)	103.6 (25.3)	99.8 (23.7)
BMI (kg/m^2)	34.4 (8.0)	36.3 (7.8)	35.0 (7.6)	35.8 (7.3)	35.4 (7.7)
SPB (mmHg)	130.5 (13.5)	129.5 (12.6)	130.2 (13.2)	130.5 (11.8)	130.2 (12.7)
DBP (mmHg)	67.3 (9.0)	68.7 (8.3)	69.7 (8.1)	68.6 (8.7)	68.6 (8.5)
Hemoglobin A_{1c} (%)	7.2 (1.2)	7.2 (0.9)	7.3 (1.0)	7.1 (1.1)	7.2 (1.0)
Baseline Laboratory Results	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*
eGFR ($mL/min/1.73\ m^2$)	31.2 (6.3)	32.9 (7.0)	33.0 (6.6)	32.3 (7.6)	32.4 (6.9)
Serum creatinine (mg/dL)	2.0(0.5)	1.0(0.5)	2.0(0.5)	2.0(0.6)	2.0(0.5)
ACR (mg/g), median (IQ range)	689 (1692)	507 (855)	656 (1131)	531 (819)	596 (1173)

Column header counts are the number of randomized patients within each group. Each line includes data only for patients with relevant data.

Table 7. Change from Baseline eGFR at Week 24 Using the Longitudinal Model

Estimates	*n*	*Change from baseline eGFR (mL/min/1.73 m^2) mean ± SE*	*Nominal 95% CI*	*p-value*
Treatment group[a]				
Bardoxolone methyl, 25 mg	57	8.3±1.1	(6.1, 10.4)	< 0.001
Bardoxolone methyl, 75 mg	57	11.5±1.1	(9.3, 13.7)	< 0.001
Bardoxolone methyl, 150 mg	56	10.6±1.1	(8.4, 12.7)	< 0.001
Combined bardoxolone methyl, all doses	170	10.1±0.6	(8.9, 11.4)	< 0.001
Placebo	57	0.1±1.1	(-2.0, 2.2)	0.92
Differences between bardoxolone methyl and placebo[b]				
Bardoxolone methyl, 25 mg	57 vs. 57	8.2±1.5	(4.5, 11.8)	< 0.001
Bardoxolone methyl, 75 mg	57 vs. 57	11.4±1.5	(7.8, 15.0)	< 0.001
Bardoxolone methyl, 150 mg	56 vs. 57	10.5±1.5	(6.8, 14.1)	< 0.001
Combined bardoxolone methyl	170 vs. 57	10.0±1.3	(7.5, 12.5)	< 0.001

The estimates come from a longitudinal model with (1) post-baseline measurements as the response variable; (2) treatment group, time, treatment group by time interaction, and continuous covariates (baseline eGFR, hemoglobin A1c, and ACR); and (3) a Toeplitz covariance structure.

a. Each p-value comes from a test comparing the mean changes to zero.

b. Each p-value comes from a test comparing the difference in means between one bardoxolone methyl group and placebo.

Table 8. Changes in weight from baseline to Week 52

		Bardoxolone methyl		
Change in weight	*Placebo N=52 n (%)*	*25 mg N=48 n (%)*	*75 mg N=48 n (%)*	*150 mg N=45 n (%)*
Increase				
> 5 kg	4 (8)	0	0	1 (2)
within 5 kg	18 (35)	5 (10)	4 (8)	2 (4)
Decrease				
within 5 kg	19 (37)	8 (17)	12 (25)	8 (18)
> 5 kg	11 (21)	35 (73)	32 (67)	34 (76)
> 10 kg	3 (6)	16 (33)	14 (29)	22 (49)
> 15 kg	2 (4)	9 (19)	4 (8)	12 (27)
Column header N counts (and denominators for calculating percentages) are the number of treated patients within each randomized group having both baseline and Week 52 weight results.				

Table 9. Weight over Time

	Weight (kg)								*Change from baseline weight (kg)*							
			Bardoxolone methyl								*Bardoxolone methyl*					
	Placebo		*25 mg*		*75 mg*		*150 mg*		*Placebo*		*25 mg*		*75 mg*		*150 mg*	
Timepoint	*n*	*Mean (95% CI)*	*n*	*Mean (95% CI)*	*n*	*Mean (95% CI)*	*n*	*Mean (95% CI)*	*n*	*Mean (95% CI)*	*n*	*Mean (95% CI)*	*n*	*Mean (95% CI)*	*n*	*Mean (95% CI)*
Baseline	57	95.2 (89.1, 101.3)	57	103.0 (96.9, 109.1)	57	97.7 (91.5, 103.8)	56	103.6 (96.8, 110.3)	--	--	--	--	--	--	--	--
Week 4	56	94.9 (88.8, 101.0)	54	102.9 (96.8, 109.0)	56	95.7 (89.7, 101.7)	55	102.0 (95.2, 108.9)	56	-0.2 (-0.6, 0.3)	54	-1.4 (-1.9, -0.9)	56	-1.4 (-2.0, -0.8)	55	-1.3 (-2.1, -0.6)
Week 8	55	94.6 (88.4, 100.7)	53	102.0 (95.8, 108.2)	52	94.8 (88.8, 100.8)	55	101.2 (94.4, 108.1)	55	0.1 (-0.5, 0.8)	53	-2.7 (-3.3, -2.1)	52	-2.6 (-3.5, -1.7)	55	-2.1 (-2.7, -1.5)
Week 12	52	94.5 (87.9, 101.1)	52	101.0 (94.6, 107.5)	52	94.0 (88.1, 99.9)	54	100.3 (93.5, 107.2)	52	-0.2 (-1.1, 0.7)	52	-3.9 (-4.8, -3.1)	52	-3.4 (-4.2, -2.6)	54	-3.3 (-4.2, -2.5)
Week 16	54	94.9 (88.5, 101.2)	52	100.0 (93.6, 106.4)	53	91.7 (85.7, 97.6)	53	98.1 (91.3, 104.8)	54	-0.3 (-1.1, 0.6)	52	-4.3 (-5.3, -3.4)	53	-4.1 (-5.0, -3.1)	53	-3.9 (-4.8, -2.9)
Week 20	54	94.9 (88.6, 101.2)	50	99.8 (93.0, 106.6)	52	92.0 (86.1, 97.9)	52	96.7 (89.8, 103.6)	54	-0.3 (-1.4, 0.9)	50	-5.0 (-6.1, -3.8)	52	-4.4 (-5.5, -3.3)	52	-5.0 (-6.1, -3.8)
Week 24	53	95.0 (88.4, 101.5)	51	98.5 (91.9, 105.0)	52	91.7 (85.9, 97.6)	51	95.5 (88.6, 102.4)	53	0.0 (-1.2, 1.1)	51	-5.9 (-7.1, -4.7)	52	-4.7 (-5.8, -3.5)	51	-5.8 (-7.1, -4.6)
Week 28	52	95.0 (88.4, 101.6)	49	98.0 (91.3, 104.8)	50	91.8 (85.7, 97.8)	47	95.1 (87.7, 102.4)	52	-0.2 (-1.4, 1.0)	49	-6.3 (-7.7, -4.9)	50	-5.1 (-6.4, -3.8)	47	-6.7 (-8.1, -5.2)
Week 32	52	94.6 (88.1, 101.2)	49	97.9 (91.1, 104.7)	48	91.6 (85.4, 97.8)	47	94.1 (86.8, 101.3)	52	-0.6 (-1.9, 0.7)	49	-6.7 (-8.2, -5.3)	48	-6.2 (-7.6, -4.7)	47	-7.2 (-8.8, -5.7)
Week 36	53	95.1 (88.6, 101.6)	46	96.9 (90.1, 103.8)	49	91.0 (84.9, 97.1)	48	95.7 (88.1, 103.2)	53	-0.3 (-1.6, 0.9)	46	-7.4 (-9.1, -5.7)	49	-6.1 (-7.6, -4.5)	48	-8.1 (-9.7, -6.5)
Week 40	53	95.0 (88.5, 101.5)	47	96.8 (90.3, 103.3)	50	90.6 (84.7, 96.6)	46	95.2 (87.4, 103.0)	53	-0.5 (-1.8, 0.8)	47	-7.9 (-9.6, -6.1)	50	-6.5 (-8.1, -5.0)	46	-8.7 (-10.4, -7.0)
Week 44	51	94.6 (87.9, 101.3)	48	96.1 (89.6, 102.5)	48	90.8 (84.5, 97.0)	45	94.7 (86.8, 102.6)	51	-0.7 (-2.0, 0.6)	48	-8.2 (-10.2, -6.3)	48	-6.9 (-8.5, -5.3)	45	-9.2 (-11.0, -7.4)
Week 48	53	94.3 (87.9, 100.7)	48	95.5 (89.1, 101.9)	47	90.4 (84.0, 96.7)	46	94.4 (86.7, 102.1)	53	-1.1 (-2.4, 0.1)	48	-8.8 (-10.8, -6.8)	47	-7.4 (-9.1, -5.7)	46	-10 (-12.2, -7.8)

	Weight (kg)								Change from baseline weight (kg)							
			Bardoxolone methyl								Bardoxolone methyl					
	Placebo		25 mg		75 mg		150 mg		Placebo		25 mg		75 mg		150 mg	
Timepoint	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
Week 52	52	92.9 (86.1, 99.8)	48	95.0 (88.6, 101.5)	48	90.0 (83.9, 96.2)	45	94.5 (86.7, 102.3)	52	-2.4 (-4.8, 0.0)	48	-9.3 (-11.4, -7.1)	48	-7.7 (-9.4, -5.9)	45	-10 (-12.3, -7.8)
Week 56	51	92.9 (86.4, 99.3)	46	97.2 (90.4, 104.0)	43	90.7 (84.5, 97.0)	40	93.6 (85.3, 102.0)	51	-1.6 (-3.1, -0.0)	46	-7.7 (-9.9, -5.6)	43	-7.6 (-9.4, -5.9)	40	-9.6 (-11.7, -7.4)
For mean weight, the number of treated patients within each randomized group who have measurements at that timepoint is displayed. For change from baseline weight, the number of treated patients within each randomized group who have both a baseline and a post-baseline measurement at that time is displayed.																

* * * * * * * * * * * * * * * *

All of the methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

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CLAIMS

Claim 1. A method of reducing weight in a subject in need thereof comprising administering to the subject an antioxidant inflammation modulator (AIM) in an amount sufficient to reduce the subject's weight.

Claim 2. The method of claim 1, where the subject has excess body fat.

Claim 3. The method of claim 1, where the subject is overweight.

Claim 4. The method of claim 1, where the subject's body mass index (BMI) is from 25 kg/m^2 to 30 kg/m^2.

Claim 5. The method of claim 1, where the subject is obese or exhibits one of more symptoms of obesity.

Claim 6. The method of claim 5, where the obesity is class I.

Claim 7. The method of claim 1, where the subject's BMI is from 30 kg/m^2 to 35 kg/m^2.

Claim 8. The method of claim 5, where the obesity is class II.

Claim 9. The method of claim 1, where the subject's BMI is from 35 kg/m^2 to 40 kg/m^2.

Claim 10. The method of claim 5, where the obesity is class III.

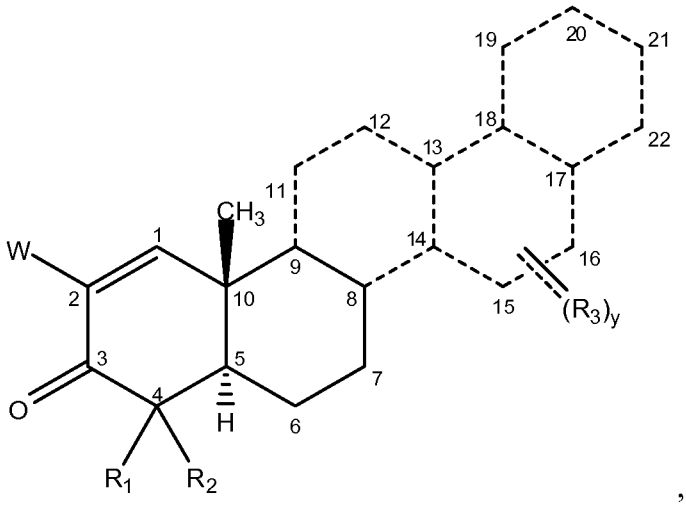
Claim 11. The method of claim 1, where the subject's BMI is from 40 kg/m^2 to 80 kg/m^2.

Claim 12. The method according to any one of claims 1-11, wherein the subject is a human subject.

Claim 13. The method according to any one of claims 1-13, wherein the method also selectively induces Nrf2 in the subject.

Claim 14. The method according to any one of claims 1-13, wherein the method also inhibits activation of NF-κB in the subject.

Claim 15. The method according to any one of claims 1-13, wherein said AIM is a compound of the formula:



,

wherein:

W is an electron withdrawing group;

R_1 and R_2 are each independently:

hydrogen, hydroxy, $alkyl_{(C\leq 8)}$, substituted $alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, substituted $alkenyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$ or substituted $alkoxy_{(C\leq 8)}$; or

R_1 and R_2 are taken together and are $alkanediyl_{(C\leq 18)}$, $alkenediyl_{(C\leq 18)}$, $arenediyl_{(C\leq 18)}$, $alkoxydiyl_{(C\leq 18)}$, $alkenyloxydiyl_{(C\leq 18)}$, $alkylaminodiyl_{(C\leq 18)}$, $alkenylaminodiyl_{(C\leq 18)}$, or $alkenylaminooxydiyl_{(C\leq 18)}$;

each R_3 is independently:

hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio;

$alkyl_{(C\leq 12)}$, $alkenyl_{(C\leq 12)}$, $alkynyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $alkylidene_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$, $alkenyloxy_{(C\leq 12)}$, $alkynyloxy_{(C\leq 12)}$, $aryloxy_{(C\leq 12)}$, $aralkoxy_{(C\leq 12)}$, $heteroaryloxy_{(C\leq 12)}$, $heteroaralkoxy_{(C\leq 12)}$, $acyloxy_{(C\leq 12)}$, $alkylamino_{(C\leq 12)}$, $dialkylamino_{(C\leq 12)}$, $alkoxyamino_{(C\leq 12)}$, $alkenylamino_{(C\leq 12)}$, $alkynylamino_{(C\leq 12)}$, $arylamino_{(C\leq 12)}$, $aralkylamino_{(C\leq 12)}$, $heteroarylamino_{(C\leq 12)}$, $heteroaralkylamino_{(C\leq 12)}$, $alkylsulfonylamino_{(C\leq 12)}$, $amido_{(C\leq 12)}$, $alkylimino_{(C\leq 12)}$, $alkenylimino_{(C\leq 12)}$, $alkynylimino_{(C\leq 12)}$,

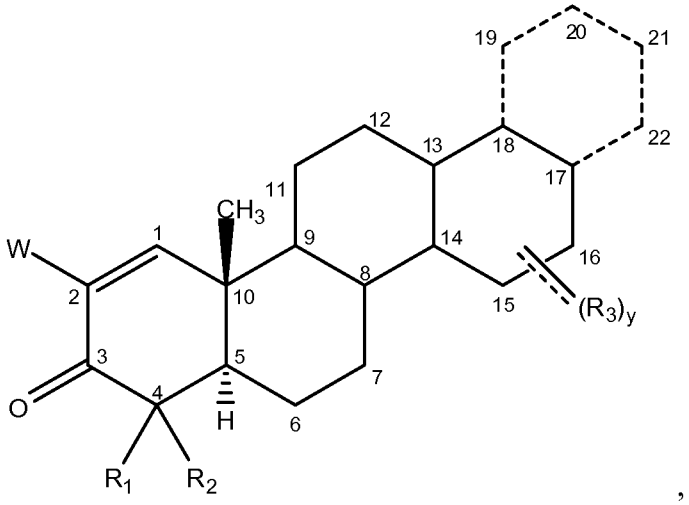
arylimino$_{(C\leq12)}$, aralkylimino$_{(C\leq12)}$, heteroarylimino$_{(C\leq12)}$, heteroaralkylimino$_{(C\leq12)}$, acylimino$_{(C\leq12)}$ or a substituted version of any of these groups; or

any two R_3 in $(R_3)_y$ are taken together and are alkanediyl$_{(C\leq18)}$, alkenediyl$_{(C\leq18)}$, arenediyl$_{(C\leq18)}$, alkoxydiyl$_{(C\leq18)}$, alkenyloxydiyl$_{(C\leq18)}$, alkylaminodiyl$_{(C\leq18)}$, alkenylaminodiyl$_{(C\leq18)}$, or alkenylaminooxydiyl$_{(C\leq18)}$; and

y is from 0 to 8;

or a pharmaceutically-acceptable salt or tautomer of the formula.

Claim 16. The method according to any one of claims 15, wherein said AIM is a compound of the formula:



,

wherein:

W is an electron withdrawing group;

R_1 and R_2 are each independently:

hydrogen, hydroxy, alkyl$_{(C\leq8)}$, substituted alkyl$_{(C\leq8)}$, alkenyl$_{(C\leq8)}$, substituted alkenyl$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$ or substituted alkoxy$_{(C\leq8)}$; or

R_1 and R_2 are taken together and are alkanediyl$_{(C\leq18)}$, alkenediyl$_{(C\leq18)}$, arenediyl$_{(C\leq18)}$, alkoxydiyl$_{(C\leq18)}$, alkenyloxydiyl$_{(C\leq18)}$, alkylaminodiyl$_{(C\leq18)}$, alkenylaminodiyl$_{(C\leq18)}$, or alkenylaminooxydiyl$_{(C\leq18)}$;

each R_3 is independently:

hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio;

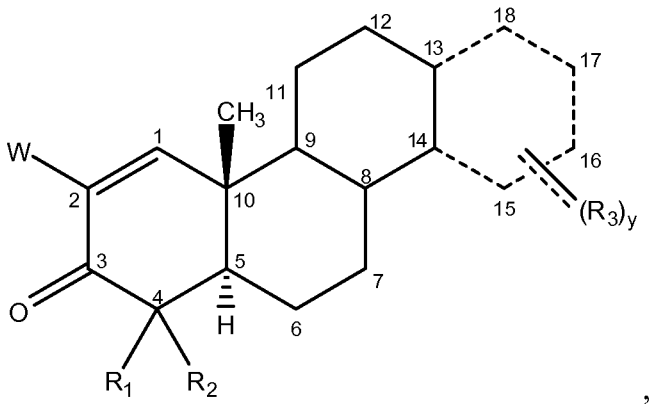
$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkylidene_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $alkenyloxy_{(C\leq12)}$, $alkynyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heteroaralkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkoxyamino_{(C\leq12)}$, $alkenylamino_{(C\leq12)}$, $alkynylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $heteroaralkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, $alkylimino_{(C\leq12)}$, $alkenylimino_{(C\leq12)}$, $alkynylimino_{(C\leq12)}$, $arylimino_{(C\leq12)}$, $aralkylimino_{(C\leq12)}$, $heteroarylimino_{(C\leq12)}$, $heteroaralkylimino_{(C\leq12)}$, $acylimino_{(C\leq12)}$ or a substituted version of any of these groups; or

any two R_3 in $(R_3)_y$ are taken together and are $alkanediyl_{(C\leq18)}$, $alkenediyl_{(C\leq18)}$, $arenediyl_{(C\leq18)}$, $alkoxydiyl_{(C\leq18)}$, $alkenyloxydiyl_{(C\leq18)}$, $alkylaminodiyl_{(C\leq18)}$, $alkenylaminodiyl_{(C\leq18)}$, or $alkenylaminooxydiyl_{(C\leq18)}$; and

y is from 0 to 8;

or a pharmaceutically-acceptable salt or tautomer of the formula.

Claim 17. The method according to any one of claims 15, wherein said AIM is a compound of the formula:



,

wherein:

W is an electron withdrawing group;

R_1 and R_2 are each independently:

hydrogen, hydroxy, $alkyl_{(C\leq 8)}$, substituted $alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, substituted $alkenyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$ or substituted $alkoxy_{(C\leq 8)}$; or

R_1 and R_2 are taken together and are $alkanediyl_{(C\leq 18)}$, $alkenediyl_{(C\leq 18)}$, $arenediyl_{(C\leq 18)}$, $alkoxydiyl_{(C\leq 18)}$, $alkenyloxydiyl_{(C\leq 18)}$, $alkylaminodiyl_{(C\leq 18)}$, $alkenylaminodiyl_{(C\leq 18)}$, or $alkenylaminooxydiyl_{(C\leq 18)}$;

each R_3 is independently:

hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio;

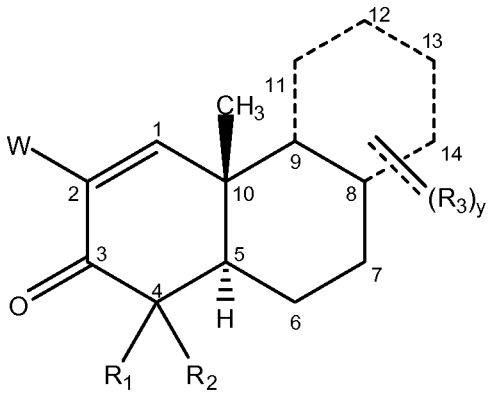
$alkyl_{(C\leq 12)}$, $alkenyl_{(C\leq 12)}$, $alkynyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $alkylidene_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$, $alkenyloxy_{(C\leq 12)}$, $alkynyloxy_{(C\leq 12)}$, $aryloxy_{(C\leq 12)}$, $aralkoxy_{(C\leq 12)}$, $heteroaryloxy_{(C\leq 12)}$, $heteroaralkoxy_{(C\leq 12)}$, $acyloxy_{(C\leq 12)}$, $alkylamino_{(C\leq 12)}$, $dialkylamino_{(C\leq 12)}$, $alkoxyamino_{(C\leq 12)}$, $alkenylamino_{(C\leq 12)}$, $alkynylamino_{(C\leq 12)}$, $arylamino_{(C\leq 12)}$, $aralkylamino_{(C\leq 12)}$, $heteroarylamino_{(C\leq 12)}$, $heteroaralkylamino_{(C\leq 12)}$, $alkylsulfonylamino_{(C\leq 12)}$, $amido_{(C\leq 12)}$, $alkylimino_{(C\leq 12)}$, $alkenylimino_{(C\leq 12)}$, $alkynylimino_{(C\leq 12)}$, $arylimino_{(C\leq 12)}$, $aralkylimino_{(C\leq 12)}$, $heteroarylimino_{(C\leq 12)}$, $heteroaralkylimino_{(C\leq 12)}$, $acylimino_{(C\leq 12)}$ or a substituted version of any of these groups; or

any two R_3 in $(R_3)_y$ are taken together and are $alkanediyl_{(C\leq 18)}$, $alkenediyl_{(C\leq 18)}$, $arenediyl_{(C\leq 18)}$, $alkoxydiyl_{(C\leq 18)}$, $alkenyloxydiyl_{(C\leq 18)}$, $alkylaminodiyl_{(C\leq 18)}$, $alkenylaminodiyl_{(C\leq 18)}$, or $alkenylaminooxydiyl_{(C\leq 18)}$; and

y is from 0 to 7;

or a pharmaceutically-acceptable salt or tautomer of the formula.

Claim 18. The method according to any one of claims 15, wherein said AIM is a compound of the formula:



,

wherein:

W is an electron withdrawing group;

R_1 and R_2 are each independently:

hydrogen, hydroxy, $alkyl_{(C\leq 8)}$, substituted $alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, substituted $alkenyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$ or substituted $alkoxy_{(C\leq 8)}$; or

R_1 and R_2 are taken together and are $alkanediyl_{(C\leq 18)}$, $alkenediyl_{(C\leq 18)}$, $arenediyl_{(C\leq 18)}$, $alkoxydiyl_{(C\leq 18)}$, $alkenyloxydiyl_{(C\leq 18)}$, $alkylaminodiyl_{(C\leq 18)}$, $alkenylaminodiyl_{(C\leq 18)}$, or $alkenylaminooxydiyl_{(C\leq 18)}$;

each R_3 is independently:

hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio;

$alkyl_{(C\leq 12)}$, $alkenyl_{(C\leq 12)}$, $alkynyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $alkylidene_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$, $alkenyloxy_{(C\leq 12)}$, $alkynyloxy_{(C\leq 12)}$, $aryloxy_{(C\leq 12)}$, $aralkoxy_{(C\leq 12)}$, $heteroaryloxy_{(C\leq 12)}$, $heteroaralkoxy_{(C\leq 12)}$, $acyloxy_{(C\leq 12)}$, $alkylamino_{(C\leq 12)}$, $dialkylamino_{(C\leq 12)}$, $alkoxyamino_{(C\leq 12)}$, $alkenylamino_{(C\leq 12)}$, $alkynylamino_{(C\leq 12)}$, $arylamino_{(C\leq 12)}$, $aralkylamino_{(C\leq 12)}$, $heteroarylamino_{(C\leq 12)}$, $heteroaralkylamino_{(C\leq 12)}$, $alkylsulfonylamino_{(C\leq 12)}$, $amido_{(C\leq 12)}$, $alkylimino_{(C\leq 12)}$, $alkenylimino_{(C\leq 12)}$, $alkynylimino_{(C\leq 12)}$, $arylimino_{(C\leq 12)}$, $aralkylimino_{(C\leq 12)}$, $heteroarylimino_{(C\leq 12)}$,

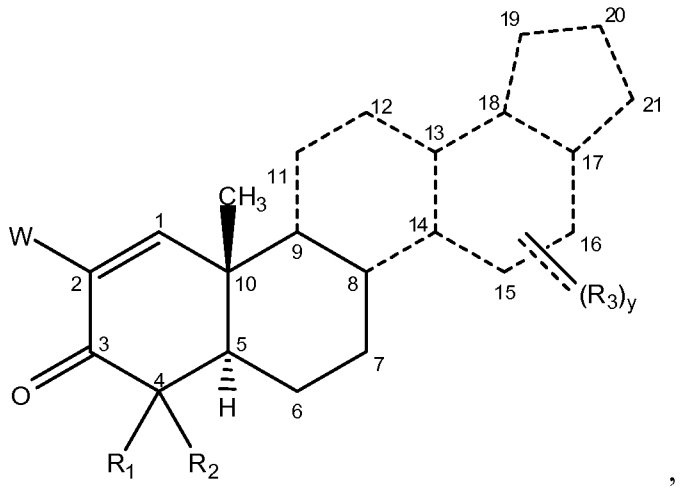
heteroaralkylimino$_{(C\leq12)}$, acylimino$_{(C\leq12)}$ or a substituted version of any of these groups; or

any two R_3 in $(R_3)_y$ are taken together and are alkanediyl$_{(C\leq18)}$, alkenediyl$_{(C\leq18)}$, arenediyl$_{(C\leq18)}$, alkoxydiyl$_{(C\leq18)}$, alkenyloxydiyl$_{(C\leq18)}$, alkylaminodiyl$_{(C\leq18)}$, alkenylaminodiyl$_{(C\leq18)}$, or alkenylaminooxydiyl$_{(C\leq18)}$; and

y is from 0 to 6;

or a pharmaceutically-acceptable salt or tautomer of the formula.

Claim 19. The method according to any one of claims 1-13, wherein said AIM is a compound of the formula:



,

wherein:

W is an electron withdrawing group;

R_1 and R_2 are each independently:

hydrogen, hydroxy, alkyl$_{(C\leq8)}$, substituted alkyl$_{(C\leq8)}$, alkenyl$_{(C\leq8)}$, substituted alkenyl$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$ or substituted alkoxy$_{(C\leq8)}$; or

R_1 and R_2 are taken together and are alkanediyl$_{(C\leq18)}$, alkenediyl$_{(C\leq18)}$, arenediyl$_{(C\leq18)}$, alkoxydiyl$_{(C\leq18)}$, alkenyloxydiyl$_{(C\leq18)}$, alkylaminodiyl$_{(C\leq18)}$, alkenylaminodiyl$_{(C\leq18)}$, or alkenylaminooxydiyl$_{(C\leq18)}$;

each R_3 is independently:

hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio;

alkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heteroaralkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkylidene$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, alkenyloxy$_{(C\leq12)}$, alkynyloxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, heteroaralkoxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, alkoxyamino$_{(C\leq12)}$, alkenylamino$_{(C\leq12)}$, alkynylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, heteroaralkylamino$_{(C\leq12)}$, alkylsulfonylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, alkylimino$_{(C\leq12)}$, alkenylimino$_{(C\leq12)}$, alkynylimino$_{(C\leq12)}$, arylimino$_{(C\leq12)}$, aralkylimino$_{(C\leq12)}$, heteroarylimino$_{(C\leq12)}$, heteroaralkylimino$_{(C\leq12)}$, acylimino$_{(C\leq12)}$ or a substituted version of any of these groups; or

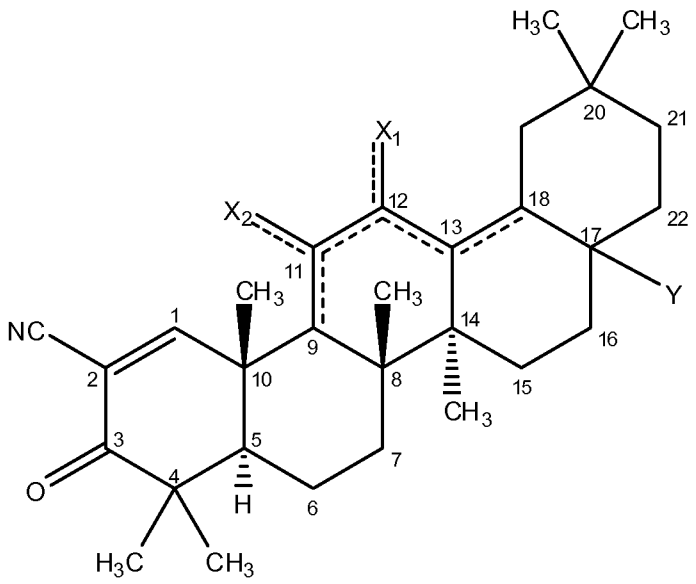
any two R_3 in $(R_3)_y$ are taken together and are alkanediyl$_{(C\leq18)}$, alkenediyl$_{(C\leq18)}$, arenediyl$_{(C\leq18)}$, alkoxydiyl$_{(C\leq18)}$, alkenyloxydiyl$_{(C\leq18)}$, alkylaminodiyl$_{(C\leq18)}$, alkenylaminodiyl$_{(C\leq18)}$, or alkenylaminooxydiyl$_{(C\leq18)}$; and

y is from 0 to 8;

or a pharmaceutically-acceptable salt or tautomer of the formula.

Claim 20. The method of any one of claims 15 to 19, wherein W is cyano, fluoro or $-CF_3$.

Claim 21. The method of claim 15, wherein said AIM is a compound of the formula:



wherein:

X_1 and X_2 are independently:

hydrogen, hydroxy, halo, oxo, amino, hydroxyamino, nitro, imino, cyano, azido, mercapto, or thio; or

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkylidene_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $alkenyloxy_{(C\leq12)}$, $alkynyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heteroaralkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkoxyamino_{(C\leq12)}$, $alkenylamino_{(C\leq12)}$, $alkynylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $heteroaralkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, $alkylimino_{(C\leq12)}$, $alkenylimino_{(C\leq12)}$, $alkynylimino_{(C\leq12)}$, $arylimino_{(C\leq12)}$, $aralkylimino_{(C\leq12)}$, $heteroarylimino_{(C\leq12)}$, $heteroaralkylimino_{(C\leq12)}$, $acylimino_{(C\leq12)}$ or a substituted version of any of these groups;

Y is hydrogen, hydroxy, halo, amino, hydroxyamino, nitro, cyano, azido, mercapto, $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $alkenyloxy_{(C\leq12)}$, $alkynyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heteroaralkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkoxyamino_{(C\leq12)}$, $alkenylamino_{(C\leq12)}$, $alkynylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $heteroaralkylamino_{(C\leq12)}$ or $alkylsulfonylamino_{(C\leq12)}$; and

or a pharmaceutically-acceptable salt or tautomer of the formula.

Claim 22. The method of claim 21, wherein said AIM is bardoxolone methyl.

Claim 23. The method of claim 22, wherein at least a portion of the bardoxolone methyl is present as a crystalline form having an X-ray diffraction pattern (CuKα) comprising significant diffraction peaks at about 8.8, 12.9, 13.4, 14.2 and 17.4 $^{o}2\theta$.

Claim 24. The method of claim 23, wherein the X-ray diffraction pattern (CuKα) is substantially as shown in FIG. 1A or FIG. 1B.

Claim 25. The method of claim 22, wherein at least a portion of the bardoxolone methyl is present as an amorphous form having an X-ray diffraction pattern (CuKα) with a halo peak at approximately 13.5 $^{o}2\theta$, substantially as shown in FIG. 1C, and a T_g.

Claim 26. The method of claim 25, wherein the T_g value is in the range of about 120 °C to about 135 °C.

Claim 27. The method of claim 26, wherein the T_g value is in the range of about 125 °C to about 130 °C.

Claim 28. The method according to any one of claims 1-27, wherein the sufficient amount of to reduce the subject's weight is a daily dose from about 0.1 mg to about 30 mg of the AIM.

Claim 29. The method according to any one of claims 1-27, where the AIM is administered orally, intraarterially or intravenously.

Claim 30. The method according to any one of claims 1-27, where the AIM is formulated as a hard or soft capsule or a tablet.

Claim 31. The method according to any one of claims 1-27, wherein the AIM is formulated as a solid dispersion comprising (i) the compound and (ii) an excipient.

Claim 32. The method of claim 31, wherein the excipient is a methacrylic acid – ethyl acrylate copolymer (1:1).

Claim 33. The method according to any one of claims 1-32, where the weight of the subject has been measured or will be measured.

Claim 34. The method of claim 33, where the weight of the subject has been measured prior to administering the AIM and will be measured after administering the AIM.

Claim 35. The method according to any one of claims 1-32, where the BMI of the subject has been measured or will be measured.

Claim 36. The method of claim 35, where the BMI of the subject has been measured prior to administering the AIM and will be measured after administering the AIM.

Claim 37. The method according to any one of claims 1-36, wherein the subject also suffers from renal disease, cardiovascular disease, diabetes, autoimmune disease, respiratory disease, neurodegenerative disease, liver disease, infectious disease, cancer or has or will undergo transplant.

Claim 38. The method according to any one of claims 1-36, wherein the subject does not also suffer from renal disease, cardiovascular disease, diabetes, autoimmune disease, respiratory disease, neurodegenerative disease, liver disease, infectious disease, or cancer.

Claim 39. The method according to any one of claims 1-36, where the subject has diabetes.

Claim 40. The method according to any one of claims 1-36, where the subject does not have diabetes.

Claim 41. The method according to any one of claims 1-36, where the subject exhibits one or more symptoms of diabetes.

Claim 42. The method according to any one of claims 1-36, where the subject does not exhibit any symptoms of diabetes.

Claim 43. The method according to any one of claims 1-36, where the subject has been identified as having diabetes.

Claim 44. The method according to any one of claims 1-36, where the subject has been identified as not having diabetes.

Claim 45. The method according to any one of claims 1-36, where the level of a marker of diabetes in the subject has been measured or will be measured.

Claim 46. The method according to any one of claims 1-36, wherein the subject has elevated levels of at least one biomarker associated with diabetes, cardiovascular disease, renal disease, fatty liver disease or metabolic syndrome.

Claim 47. The method according to any one of claims 1-36, wherein the subject does not have elevated levels of at least one biomarker associated with diabetes, cardiovascular disease, renal disease, fatty liver disease or metabolic syndrome.

Claim 48. The method according to any one of claims 1-36, wherein the subject does not have elevated levels of any biomarker associated with diabetes, cardiovascular disease, renal disease, fatty liver disease or metabolic syndrome.

Claim 49. The method according to claims 46 or 47, wherein the biomarker is a marker of insulin resistance, leptin resistance, adiponectin resistance, cardiovascular stress, or renal dysfunction.

Claim 50. The method of claim 49, wherein the biomarker is a marker of insulin resistance.

Claim 51. The method of claim 50, wherein the biomarker is fasting glucose or hemoglobin A1c.

Claim 52. The method of claim 49, wherein the biomarker is a marker of leptin resistance.

Claim 53. The method of claim 49, wherein the biomarker is a marker of adiponectin resistance.

Claim 54. The method of claim 53, wherein the biomarker is adiponectin.

Claim 55. The method of claim 49, wherein the biomarker is a marker of cardiovascular stress.

Claim 56. The method of claim 55, wherein the biomarker is circulating endothelial cells or C-reactive protein.

Claim 57. The method of claim 55, wherein the biomarker is circulating endothelial cells.

Claim 58. The method of claim 57, wherein the biomarker is iNOS-positive circulating endothelial cells.

Claim 59. The method of claim 49, wherein the biomarker is a marker of renal disease.

Claim 60. The method of claim 59, wherein the biomarker is serum creatinine.

Claim 61. The method of claim 59, wherein the biomarker is cystatin C.

Claim 62. The method of claim 59, wherein the biomarker is uric acid.

Claim 63. The method according to any one of claims 1-36, where the subject has chronic kidney disease (CKD) or exhibits one or more symptoms of CKD.

Claim 64. The method according to any one of claims 1-36, where the subject does not have chronic kidney disease (CKD)

Claim 65. The method according to any one of claims 1-36, where the subject does not exhibit any symptoms of CKD.

Claim 66. The method according to any one of claims 1-36, where the subject has been identified as having CKD.

Claim 67. The method according to any one of claims 1-36, where the subject has been identified as not having CKD.

Claim 68. The method according to any one of claims 1-36, where the level of a marker of CKD in the subject has been measured or will be measured.

Claim 69. The method according to any one of claims 63-67, where the CKD is characterized by a serum creatinine level of 1.3-3.0 mg/DL where the subject is a human female or a serum creatinine level of 1.5-3.0 mg/DL where the subject is a human male.

Claim 70. The method of claim 63, where the CKD is stage 4.

Claim 71. The method according to any one of claims 1-36, where the subject does not have stage 4 chronic kidney disease (CKD).

Claim 72. The method according to any one of claims 1-36, where the subject has diabetic nephropathy (DN) or exhibits one or more symptoms of DN.

Claim 73. The method according to any one of claims 1-36, where the subject does not have diabetic nephropathy (DN)

Claim 74. The method according to any one of claims 1-36, where the subject does not exhibit any symptoms of DN.

Claim 75. The method of claim 72, where the subject has been identified as having DN.

Claim 76. The method of claim 72, where the subject has been identified as not having DN.

Claim 77. The method according to any one of claims 1-36, where the level of a marker of DN in the subject has been measured or will be measured.

Claim 78. The method according to any one of claims 1-36, where the administering results in an improvement in estimated glomerular filtration rate (eGFR) of the subject.

Claim 79. The method of claim 78, where the administering reduces the level of serum creatinine in the subject.

Claim 80. The method of claim 79, where the level of serum creatinine in the blood of the subject has been measured or will be measured.

Claim 81. The method according to any one of claims 1-36, where the level of blood urea nitrogen (BUN) in the subject has been measured or will be measured.

Claim 82. The method according to any one of claims 1-36, where the level of Adiponectin in the blood of the subject has been measured or will be measured.

Claim 83. The method according to any one of claims 1-36, where the level of Angiotensin II in the subject has been measured or will be measured.

Claim 84. The method according to any one of claims 1-36, where the subject has insulin resistance or exhibits one or more symptoms of insulin resistance.

Claim 85. The method according to any one of claims 1-36, where the subject does not have insulin resistance.

Claim 86. The method according to any one of claims 1-36, where the subject does not exhibit any symptoms of insulin resistance.

Claim 87. The method of claim 84, where the subject has been identified as having insulin resistance.

Claim 88. The method of claim 85, where the subject has been identified as not having insulin resistance.

Claim 89. The method according to any one of claims 1-36, where the level of a marker of insulin resistance in the subject has been measured or will be measured.

Claim 90. The method of claim 84, where the level of hemoglobin A1c in the subject has been measured or will be measured.

Claim 91. The method of claim 84, where a blood sugar level of the subject has been measured or will be measured.

Claim 92. The method of claim 84, where the administering reduces the level of hemoglobin A1c or fasting blood glucose in the subject.

Claim 93. The method of claim 91, where a fasting glucose level of the subject has been measured or will be measured.

Claim 94. The method of claim 84, where the insulin sensitivity of the subject has been measured or will be measured by a hyperinsulinemic euglycemic clamp test.

Claim 95. The method of claim 84, where a glucose disposal rate (GDR) in the subject has been measured or will be measured.

Claim 96. The method according to any one of claims 1-36, where the subject has glucose intolerance or exhibits one or more symptoms of glucose intolerance.

Claim 97. The method according to any one of claims 1-36, where the subject does not have glucose intolerance.

Claim 98. The method according to any one of claims 1-36, where the subject does not exhibit any symptoms of glucose intolerance.

Claim 99. The method of claim 96, where the subject has been identified as having glucose intolerance.

Claim 100. The method of claim 97, where the subject has been identified as not having glucose intolerance.

Claim 101. The method according to any one of claims 1-36, where the level of a marker of glucose intolerance in the subject has been measured or will be measured.

Claim 102. The method of claim 96, where the level of hemoglobin A1c in the subject has been measured or will be measured.

Claim 103. The method of claim 96, where a blood sugar level of the subject has been measured or will be measured.

Claim 104. The method of claim 96, where the administering reduces the level of hemoglobin A1c or fasting blood glucose in the subject.

Claim 105. The method of claim 103, where a fasting glucose level of the subject has been measured or will be measured.

Claim 106. The method of claim 96, where the insulin sensitivity of the subject has been measured or will be measured by a hyperinsulinemic euglycemic clamp test.

Claim 107. The method of claim 96, where a glucose disposal rate (GDR) in the subject has been measured or will be measured.

Claim 108. The method according to any one of claims 1-36, where the subject has cardiovascular disease (CVD) or exhibits one or more symptoms of CVD.

Claim 109. The method according to any one of claims 1-36, where the subject does not have cardiovascular disease (CVD) or does not exhibit any symptoms of CVD.

Claim 110. The method according to any one of claims 1-36, where the subject does not exhibit any symptoms of CVD.

Claim 111. The method according to any one of claims 1-36, where the subject has been identified as having CVD.

Claim 112. The method according to any one of claims 1-36, where the subject has been identified as not having CVD.

Claim 113. The method according to any one of claims 1-36, where the level of a marker of CVD in the subject has been measured or will be measured.

Claim 114. The method according to any one of claims 1-36, where the number of circulating endothelial cells (CECs) in the blood of the subject has been measured or will be measured.

Claim 115. The method of claim 114, where the CECs are iNOS-positive circulating endothelial cells.

Claim 116. The method of claim 108, where the administering also reduces the level of circulating endothelial cells in the subject.

Claim 117. The method of claim 116, where the administering also reduces the level of hemoglobin A1c or fasting blood glucose in the subject.

Claim 118. The method according to any one of claims 1-36, where the subject has fatty liver disease (FLD) or exhibits one or more symptoms of FLD.

Claim 119. The method according to any one of claims 1-36, where the subject does not have fatty liver disease (FLD) or does not exhibit any symptoms of FLD.

Claim 120. The method according to any one of claims 1-36, where the subject does not exhibit any symptoms of FLD.

Claim 121. The method according to any one of claims 1-36, where the subject has been identified as having FLD.

Claim 122. The method according to any one of claims 1-36, where the subject has been identified as not having FLD.

Claim 123. The method according to any one of claims 1-36, where the level of a marker of FLD in the subject has been measured or will be measured.

Claim 124. The method according to any one of claims 1-36, where the subject has been identified as having cancer.

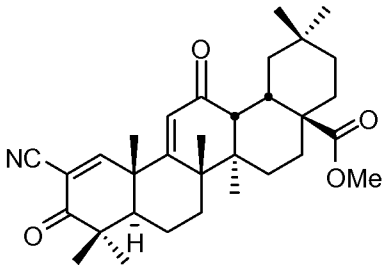
Claim 125. The method according to any one of claims 1-36, where the subject has been identified as not having cancer.

Claim 126. The method according to any one of claims 1-36, where the subject has been identified as having cancer and diabetes.

Claim 127. The method according to any one of claims 1-36, where the subject has been identified as not having cancer and diabetes.

Claim 128. The method according to any one of claims 1-36, where if the sufficient amount were administered to a non-obese subject, the non-obese subject's weight would not be reduced significantly.

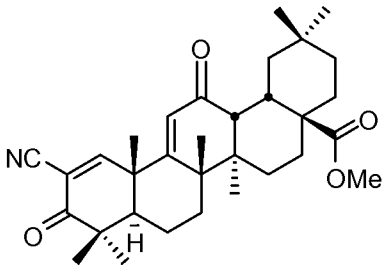
Claim 129. A method of reducing a subject's weight comprising administering to the subject a compound of the formula,



,

in an amount sufficient to reduce the subject's weight, where the subject has been identified as (i) being overweight or obese; and (ii) not having diabetes.

Claim 130. A method of reducing a subject's weight comprising administering to the subject a compound of the formula,



,

in an amount sufficient to reduce the subject's weight, wherein:

(a) at least a portion of the compound is present as an amorphous form having an X-ray diffraction pattern (CuKα) with a halo peak at approximately 13.5 °2θ, substantially as shown in FIG. 1C, and a T_g from about 120 °C to about 135 °C; and

(b) where the subject has been identified as

(i) being overweight or obese; and

(ii) not having diabetes.

Claim 131. The method of claim 130, wherein the subject is a human and the amount is a daily dose from 5 mg to 50 mg.

Claim 132. The method of claim 131, wherein the daily dose is about 10 mg.

Claim 133. The method of claim 131, wherein the daily dose is about 20 mg.

Claim 134. The method of claim 131, wherein the daily dose is about 40 mg.